THE CAUSES AND COURSE OF NEPHRITIS.

In spite of a great amount of research work, the number of unsolved problems connected with nephritis remains considerable, and the field for further investigation remains so obviously wide that the choice of this particular subject for a research does not seem to require any special justification. It was on the advice of, and with the encouragement of, Professor Shennan that I undertook this work.

A first impression was of the multiplicity of the problems presented, and it soon became evident that attention would have to be focussed chiefly on one or two of these.

Of our outstanding difficulties in an understanding of nephritis, two are perhaps of more fundamental interest than any of the others. In the first place, the actual cause or causes have never been ascertained with certainty, and, secondly, a clear idea of the process of

development of the disease is wanting.

To the first of these problems, some attention has been paid in this research, but in great part efforts were directed towards an understanding of the second point.

It was not possible, however, to consider the process of development of nephritis without a preliminary study of etiological considerations.

The thesis which follows will therefore be divided into two main sections. In the first section, statistical, clinical and post-mortem evidence will be sought for, and conclusions will mainly be related to etiology, whereas in the second section experimental evidence, derived both from the literature and from personal experiments, will be examined to see what light may be thrown on the etiology and course, and to determine to what extent such experimental findings may be applicable to the disease as it occurs in man.

One important point must be made clear at the outset, however. Where the contrary is not specially indicated we mean by nephritis non-suppurative Bright's disease, and do not therefore include all inflammations of the kidney. The use

of the unqualified term "nephritis" in this restricted sense is a matter of very widespread custom, but we mention the point particularly as we shall be frequently contrasting "nephritis" in various ways with "suppurative nephritis."

SECTION I.

STATISTICAL, CLINICAL AND POST-MORTEM EVIDENCE.

Evidence of the above nature may be considered under a number of heads. From the first we are confronted with the enormous bulk of ordinary clinical experience which assures us of certain definite associations of acute nephritis, these associations in themselves pointing very strongly to a number of bacterial or toxic substances as being possibly factors, if not necessarily the only ones.

An association of acute nephritis with quite a number of diseases has long been claimed. Of these scarlet fever is usually held to show the association most commonly, though the actual figures given by different writers vary enormously. Osler gives the range as from 10% - 20%, whereas Claude Ker, in one series of cases, found an incidence of 8.78%. Acute nephritis is, however, described as occurring with significant frequency in many other diseases. A fairly typical list is that of Professor Gulland (from his systematic lectures in Medicine). It is given here with the bracketed opinions of Osler (123) or Claude Ker (74) as these are expressed in their

respective text books.

Measles ("Not very uncommon" - Osler. "Very uncommon" has "seen only two cases" - Claude Ker.)

Smallpox ("Rare" - Osler.)

Malaria ("4.5% of aestivo-autumnal cases" - Osler.)

Pneumonia ("Not often" - Osler.)

Meningitis

Typhoid ("Occurs" - Osler.)

Endocarditis (This is emphasised by many writers, but we shall see later that here we are often dealing with a special type of the disease.)

The list is variously amplified or modified by different writers. It is interesting to note, even at this point, how rapidly opinions conflict whenever we leave scarlet fever. Although all the diseases in the above list may be found inculpated in one text-book or another, on hardly one is the verdict unanimous. This difference of opinion is partly due to the varying standards adopted in the definition of nephritis. Most exclude from the definition milder albuminurias without other evident renal symptoms ("febrile" albuminurias, etc.). These are common, though in varying percentages, in all the fevers mentioned, and, indeed, in many other fevers.

That they represent the operation in milder degree of the same causes as at other times

lead to acute nephritis can scarcely be doubted. At one time the tendency was to regard them as due to the coexisting high temperature, but the repeated recovery of organisms from the urine in such cases suggests a much more satisfactory alternative - an organismal cause (Teissier and Duvoir 168.) Even a difference in degree, however, justifies us in the separation of febrile albuminurias from acute nephritis, for, in the two groups, the severity, and, along with it, the likelihood of permanent damage, differ markedly. In the one case the clinical picture is that of an infection accompanied by an incidental albuminuria; in the other the picture is mainly that of a nephritis, and the patient's dangers are chiefly of renal origin.

Moreover, in some cases there may be a little more than a difference solely of degree, for in scarlet fever at least, where both conditions are common, febrile albuminuria occurs at an early stage accompanying severe general symptoms, whereas the true nephritis appears in the second or third week. This difference suggests the supervention of other factors. Teissier and Duvoir (160) implicate the second and third weeks as the "period of secondary infection", and conclude that the nephritis

is one of its manifestations. This is probably true to the extent that we may find the explanation of the nephritis and of the other possible complications of that period identical, but the streptococcus, which they hold to be the usual secondary invader, is probably the actual strep. scarlatinae which has caused the original disease. A further suggestion, that an anaphylactic phenomenon is at work at this stage, is a very plausible one, and may account for the whole crop of complications liable to occur at this stage. (Kinloch 76 and Claude Ker 74.).

Another source of difficulty which may partly account for differing views as to the incidence of acute nephritis in various diseases, is the great difference in the percentage of renal complications observed in different epidemics. Sometimes this variation is explicable by the variation in severity of the particular disease in question in different epidemics. At other times, however, no such correlation can be established. Thus, an epidemic of mild scarlet fever may show quite as high a percentage of nephritis as a much severer epidemic of the disease, and, further, the severity of any individual case is no criterion as to the likelihood of its developing a subsequent nephritis (Bright, Trousseau, Hase, quoted by Teissier 160).

Whatever the causes, however, of the statistical variations, it is undoubted that they are great. The variations are great even in scarlet fever, so great that it would be misleading and futile to attempt to plot an average. The figures of various authorities will be found summarised by Teissier and Duvoir (160) and vary enormously. Yet, vary as they may, it might be claimed that there is hardly a single authority who does not find a special relation to acute nephritis in this disease. Of no other disease can the same be said; and, as regards almost any other disease, we have not to seek far before we find an observer who challenges the special relation which others claim to exist between it and acute nephritis.

Occasionally, clinical cases of nephritis occur where the cause is definite but of an unusual nature. Of such a type are the nephritides due to poisoning by mercuric chloride, cantharides, turpentine, snake venom and arsenic.

The great bulk of cases of nephritis, however, come under none of the categories yet dealt with. They are, at least on superficial examination, of primary origin, and a relationship to pre-existing disease is not easily determined.

In view of the last fact we must look somewhat more critically into the nature of the occasional relationship between these diseases alleged, at times, to cause nephritis and the associated nephritis. Particularly must we do so since, when we come to examine such diseases individually, the existence of the special relationship is usually, as we have noted, not universally admitted.

With this object we sought for statistics which would cover in a uniform manner a wide range of diseases. Data fairly satisfactory for our purpose, were found in the "Medical Statistics of the United States Surgeon General" for the Great War. These comprised all medical admissions (as against war casualties) to American Army Hospitals, (in the States, in France, and elsewhere) over a period of 33 months (April 1st 1917 - December 31st 1919).

They are edited in a manner which enables one to extract from them the percentage incidence of acute and chronic nephritis in cases admitted for each and every disease. The population concerned is a large one, (up to about four millions at one time) and its type is fairly uniform.

The results, particularly as to acute nephritis, are, we think, very interesting. It was not thought that percentages of associated chronic nephritis found after admission for other diseases could necessarily be regarded as indicating a commencement of nephritis subsequent to the other disease even in regard to time of onset. On the other hand, when a patient admitted for a given disease was later found with acute nephritis also, it is highly likely that the nephritis was truly subsequent, at least as regards the time of onset. If, in addition the percentage of cases in which an acute nephritis developed in any one disease was much higher than the average percentage, it is legitimate to conclude also that the subsequent development of nephritis was here more than a chance one.

Taking all diseases (save nephritis cases) together, the percentage of complication by acute nephritis is surprisingly low (.037%) and even the highest figures are low. The low average complication may be partly due to the fact that the total admissions include a large number of relatively trifling conditions.

Basis of Classification Adopted in Abstracting the Statistics.

I. No disease is recorded separately in which there was a total of under 100 cases.

II. The Table is divided into four sections, A,B,C, and D.

III. In every case the diseases in Sections A,B and C, (i.e. the diseases followed by Acute Bright's Disease in 0.05% cases or over) are recorded individually. Thus, no disease of the International Classification adopted by the Surgeon General had an incidence of acute nephritis as high as 0.05% if it does not appear separately in one or other of these sections. Space might have been saved and much irrelevant material excluded by omission of some of these diseases or by grouping several under a common head, but it was felt that by exercising no selection in this direction the figures would be more unbiassed and therefore more convincing. (For sole exception, see "I" above.)

IV. All diseases which gave percentages under 0.05 have been grouped in Section D under broad system headings. From what has just been said in "III" it will be understood that each such heading includes only those diseases of the system concerned which individually had a percentage incidence of acute nephritis under 0.05%, the others having all been mentioned separately in one or other of the previous sections. No disease, therefore, has been included in any 'D' grouping if its incidence of acute nephritis was 0.05% or higher, (e.g. as cancer is not mentioned separately in any of Sections A,B, or C, it may be correctly assumed that the percentage of acute nephritis following it was under 0.05% and that it has been included in Section D, in this case along with other "General Diseases."

V. The table thus embodies all cases of all medical diseases admitted to all hospitals of the United States army, in all countries, during the whole period April 1st 1917 - December 31st 1919.

Section A.

This comprises a small group of conditions with a fairly high percentage association with acute nephritis, which have, however, been excluded from Sections B and C on the ground that they are conditions occurring so commonly in acute or chronic nephritis as to justify the suspicion that the statistics recorded include many cases in which a nephritis was existent prior to the condition mentioned. It is therefore obviously undesirable to include these as a true reflex of the occurrence of acute nephritis as a sequel to these conditions.

A comparison of the figures in the column giving the numbers of associated chronic nephritis, with the numbers under acute nephritis will strengthen this suspicion. In almost every instance the numbers of chronic nephritis are higher, increasing the suspicion that "acute" nephritis, when recorded, is here often merely an exacerbation of a preexisting condition.

For instance, it is very unlikely that an attack of apoplexy "initiated an acute nephritis in a previously healthy kidney".

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.	% of Cases Complicated by Chronic Nephritis.
Arterio-Sclerosis.	407	3	14	.74	3.44
Cardiac Hyper-trophy.	1,117	4	6	.36	.54
Angina Pectoris.	317	1	1	.31	.31
Apoplexy.	356	1	1	.28	.28
Organic Diseases of Heart (excluding valvular etc. in Sects.B and C.)	1,793	5	10	.28	.56
Cardiac Dilata-tion.	540	1	4	.18	.74
Cardiac Arrhyth-mias.	1,182	2	0	.17	.00
Myocard-itis and Myocard-ial Insu-fficiency	2,857	4	23	.14	.81
Enuresis.	2,882	2	3	.07	.10.

Section B.

Here are included separately all diseases (save for a few in Section A) in which the percentage development of acute nephritis was 0.3% or higher.

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.
General Septic-aemia.	199	2	1	1.00
Nephro-ptosis.	100	1	1	1.00
Acute Endocar-ditis.	367	3	0	.82
Diabetes Mellitus.	618	5	38	.81
Scarlet Fever.	11,189	84	48	.75
"Simple" Mening-itis.	486	3	4	.62
Acute Miliary T.B.	238	1	4	.42
Typhoid Fever.	1,386	4	2	.30
C.S. Mening-itis.	4,612	14	4	.30
Broncho-pneumon-ia.	30,903	93	82	.30

Section C.

Here are included individually (save for "Enuresis" in Section A) all diseases where the percentage development of acute nephritis was 0.05% or more, but under 0.30%.

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.	Remarks.
Cataract	351	1	0	.28	
Kidney & Annexa. (Unclassified Diseases*)	1,651	4	11	.24	
Lobar Pneumonia	43,127	97	86	.23	
Pulmonary Emphysema	459	1	2	.22	Probably should be in Sect.A with arterio-sclerosis.
Nephro-lithiasis.	1,385	3	2	.22	
Circulatory System (Unclassified Diseases*)	509	1	0	.20	Perhaps should be in Sect. A?
Erysipelas	2,456	5	9	.20	
Diseases Digestive System (Unclassified*)	496	1	0	.20	
Alcoholic Psychoses	536	1	1	.19	

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.
Suppurative Pleurisy.	1,635	3	14	.18
Psychasthenia	684	1	1	.15
Diseases of Lung (Unclassified*)	1,375	2	1	.15
Cystitis	3,373	5	8	.15
Simple Goiter	1,430	2	2	.14
Smallpox	794	1	2	.13
Trench Fever	743	1	1	.13
Rickets	951	1	1	.10
Valvular Diseases of Heart	16,850	17	92	.10
Carbuncle	2,163	2	1	.09
Diphtheria	10,427	8	12	.08
Diseases of Ear (Unclassified)*	1,280	1	0	.08
Dysentery	3,918	3	2	.08
Suspected T.B.	2,353	2	0	.08
"Other" T.B.	2,477	2	8	.08

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.
Osteo-myelitis	1,305	1	1	.08
Chole-cystitis	2,393	2	6	.08
Acute Articular Rheumat-ism.	23,818	16	14	.07
Neuro-Circul-atory Asthenia	4,307	3	7	.07
Diseases of Eye-lids.	1,640	1	1	.06
T.B. Lungs.	31,101	19	52	.06
General Diseases (Unclass-ified.*)	5,092	3	5	.06
Function-al Cardiac Disorders (Unclassif.*)	4,955	3	4	.06
Diseases of Pleura	15,263	9	8	.06
Measles	93,629	47	28	.05
Muscular Rheumat-ism.	11,328	6	7	.05

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.
Sero-Fibrinous Pleurisy.	4,429	2	7	.05

*Where the word "Unclassified" has been used above there has been no grouping together of diseases separately classified in the international nomenclature adopted by the Surgeon-General. Such groups are those which close his classification of each system and, presumably, consist of miscellaneous cases not easily classified individually.

Section D.

Contains the figures relating to diseases where the percentage of subsequent acute nephritis was under 0.05%. Such diseases have usually been grouped into systems, but none of the individual diseases of the system-group had itself a percentage over 0.05% (i.e. the system groups here exclude all diseases already figuring in previous sections).

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.	Remarks.
Infectious Fevers not previously mentioned.	987,243	347	311	.04	Great majority are Influenza and Mumps.
General Diseases not previously mentioned	47,853	20	56	.04	Endocrines, Tumours, Arthritis, etc.
Diseases of Ear not previously mentioned	39,175	11	23	.03	Chiefly Otitis Media.
Diseases of Respiratory System, not previously mentioned.	242,278	87	89	.03	Chiefly Bronchitis.
Diseases of Circulatory System, not previously mentioned.	61,813	10	27	.02	
All Diseases of Throat.	259,005	60	36	.02	Chiefly Tonsilitis & Pharyngitis.

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.	Remarks.
Diseases of Digestive System not previously mentioned.	297,964	51	82	.02	
Nervous System save Apoplexy & Enuresis (Sect. A).	43,746	8	19	.02	
Diseases of Skin & Cellular Tissues (save Carbuncle Sect. C).	128,912	14	23	.01	Many of these infective.
All Venereal Diseases.	338,746	19	21	.01	
Diseases of Locomotory System (save Osteomyelitis Sect. C)	76,761	10	23	.01	
Mental Aberration not previously mentioned.	37,505	4	16	.01	

Disease.	Total No. of Cases.	Absolute No. of Cases Complicated by Acute Nephritis.	Absolute No. of Cases Complicated by Chronic Nephritis.	% of Cases Complicated by Acute Nephritis.
Congenital Malformations & not specified or ill-defined Diseases.	138,075	8	3	.01
Non-Venereal Diseases of Genital System & Bladder, not previously mentioned.	24,504	2	9	.01
Diseases of Eyes and adnexa not previously mentioned.	35,925	1	15	.00
Non-Venereal Diseases of Kidney, Ureter & Perinephric Tissue, not previously mentioned.	1,007	0	8	.00
All Diseases of Nasal Fossae.	64,579	3	5	.00
TOTAL OF ALL ADMISSIONS (save primary admissions for acute & chronic nephritis).	3,187,293	1,165	-	.037

Commentary.

The statistics confirm the usual impression that in certain conditions there is a special liability to the subsequent development of acute nephritis. All conditions in Section B show a percentage occurrence of 0.30% or over as against an average incidence over all diseases of 0.037%. It seems a reasonable deduction that the relationship in these cases is more than an accidental one, for the lowest of them (0.30%) is over eight times the average for all cases, and the highest (1.0%) is twenty-seven times the average.

Reviewing them, they include General Septicaemia (Case Mortality 46.23%), Acute Endocarditis (Case Mortality 11.17%), Scarlet Fever (Case Mortality 3.02%), Simple Meningitis (Case Mortality 46.09%), Acute Miliary Tuberculosis (Case Mortality 82.35%), Typhoid Fever (Case Mortality 15.51%), Cerebro Spinal Meningitis (Case Mortality 37.66%) and Broncho-pneumonia (Case Mortality 27.90%).

The bracketed case mortalities are the actual percentage case mortalities in the statistics.

While all show a clear special relation, the case mortalities given above, taken with the percentage incidences of acute nephritis, place the relationship with scarlet fever in a special position by itself. The case mortality is much

lower than in the other diseases named* and the indication of a special susceptibility of the kidneys to the disease is therefore very much greater than in the others. These others are diseases of high case mortality, sometimes very high. All are infections; most at least are probably septicaemic. The involvement of the kidneys in the course of such relatively overwhelming conditions, while obviously not a chance one, is probably largely due to the severity of the general condition, to a mass attack as it were, and demands in explanation a much milder degree of selective action than is required to explain the incidence in the less fatal scarlet fever.

(Two other conditions complete Section B - nephroptosis, with acute nephritis in 1%, and diabetes mellitus, with acute nephritis in 0.81%. The former percentage is based on a small number of cases, but many indicate some degree of special liability of the kidney to inflammation when its circulation is interfered with. Diabetes mellitus, alone in Section B, shows a much larger number of cases of chronic than of acute nephritis (seven to eight times larger). It is possible, therefore, that some of the acute cases were exacerbations of chronic ones. In any case, however, the diabetic

*In typhoid where the case mortality approaches that in scarlet fever, the case incidence of nephritis is only 2/5 of the incidence in the latter disease (0.3% as against 0.75%).
In endocarditis a rather different type of nephritis, embolic and patchy, is apt to occur, and so raise the incidence. This special type, and its relationship to the ordinary type, will be considered later. (P. 164-5 - P. 61).

condition seems in quite a number of cases to be associated with nephritis of one kind or another. (This is supported both by clinical records and post-mortem examinations of diabetics in Aberdeen Royal Infirmary). The special relationship may depend upon a common causal factor (e.g. bacteria acting on both pancreas and kidney); upon bacterial infection of the kidney from the septic foci diabetics are so prone to develop; or perhaps in part upon the alteration in function demanded of the kidney in the disease (in which case the renal damage might be only partly inflammatory, and partly degenerative).

Passing to Section C, we find the higher incidences to include a number of infective conditions such as lobar pneumonia, but as the percentages are beginning to approach more to the average, little can be said of a special liability on the basis of this table. That we are nearing the danger line of chance er ror is hinted by the presence in this table of a few presumably non-infective conditions, where no special reason for a relationship can be ascertained, or has been maintained to exist.

Coming to Section D, some of the figures are specially interesting. Diseases of the Ear (chiefly Otitis Media), Diseases of the Throat (Pharyngitis and Tonsilitis, acute and chronic), Diseases of the Skin (excluding Carbuncle, but including a host of minor infections), and Diseases of the Nasal Fossae are all represented. None have an incidence appreciably above the total average; most are very distinctly below it. All are diseases where focal bacterial infection exists, and many are of a type (e.g. tonsilitis) which might

have been expected to give rise to acute nephritis in a raised percentage of cases were the kidneys specially susceptible to the circulating toxins, or to the organisms when they too happened to be present in the blood-stream. The explanation may be that the organisms themselves had penetrated only in rare cases into the bloodstream, and that the toxins alone were inadequate to initiate an acute nephritis. Alternatively, and further evidence from other viewpoints will tend to confirm this, the bacteriology of the infections may frequently have been unsuited to produce nephritis.

For the moment, however, we will leave this point, pausing only to recall the composition of the population studied - healthy male adults, for we will find reason later to believe that with another group - children - the predisposing influence of a similar type of focal infection is considerable.

Our conclusions might be summarised as follows:-

I. It would seem that in the adult male, diseases which give rise to acute nephritis in a significantly high percentage of cases, do so only partly by a relatively feeble selective action on the kidney, and are enabled to act mainly by the extreme virulence of the primary infection. Such diseases are infective and usually septicaemias (Section B).

II. The one exception noted to this is scarlet fever, in which the haemolytic streptococcus or its toxins seems to act in a powerfully selective manner. In passing, it may be recalled as the personal experience of most observers that the incidence of nephritis in scarlet fever does not seem to be related to t he severity of the cases.

One is therefore tempted to believe

(a) That in adult males the scarlet fever streptococcus or its toxins is the only powerfully selective renal poison discoverable by an analysis of cases of acute nephritis starting as a complication of other disease, and

(b) That it may therefore be profitable to investigate the role of the streptococcus in cases of "primary" acute nephritis, for, so far as the present evidence indicates, it suggests, not only that the streptococcus has a selective action, but that numerous other organisms do not possess such an action.

III. Contrary to a widely held belief, there is no evidence to suggest an increased liability in adults to acute nephritis in the ordinary tonsillar and other relatively slight or superficial focal infections. (N.B. The qualifications "in adults" will be explained later by the different results of an inquiry into the etiological factors in children).

There is one point noted above on which confirmatory evidence can readily be obtained from other sources, namely the existence of some relationship of very severe infection to acute nephritis. Perhaps the readiest statistical confirmation of this may be found in post-mortem records, for the very nature of the combination of diseases considered makes it easy clinically to miss the nephritis in view of the overwhelming sepsis present.

Figures illustrating the point could no doubt be compiled from any series of post-mortems. A typical group of material was examined by Shaw, Dunn and Thompson (152) who analysed 660 consecutive post-mortem records, and found thirteen cases of acute nephritis, undiagnosed clinically, and all dying of other diseases. All were cases of sepsis. (They were recorded chiefly as showing that even marked acute nephritis might occur without symptoms of renal insufficiency being detected during life, but it is the relationship to sepsis that we are concerned with just now). Shaw Dunn regarded the findings as showing that, whilst sepsis need not in most cases give rise to more than moderate toxic changes in the kidneys, it did on occasion give rise to acute nephritis.

We have examined the post-mortem records of Aberdeen Royal Infirmary for the past year (1926) in a somewhat similar manner.

Of 170 consecutive post-mortems 91 were classified as showing a prominent septic or infective element. The standard of "prominence" is of course bound to be rather arbitrary, but all sepsis or acute infection which materially contributed to the fatal issue has been included.

Of these 91 cases, only 4 showed acute nephritis. None of the 4 cases were diagnosed clinically. In non-septic and non-infectious cases there were no cases of acute nephritis not diagnosed clinically. There were however 2 cases of clinically diagnosed acute nephritis, one of them showing no other important disease, the other accompanied by diabetes mellitus. There can thus be no doubt that quite an important fraction of the total number of cases of acute nephritis are associated with fatal sepsis, although clinically the fact cannot be readily established because the patient is suffering chiefly from the acute sepsis, and eventually dies of this. On the other hand, there is as little doubt that the great majority of cases even of fatal sepsis do not cause acute nephritis, and that acute nephritis, where present in sepsis, indicates either a special bacteriology responsible for the sepsis, or is directly dependent on the severity of the infection. The organisms present in most cases of acute sepsis are not likely, therefore, to be suitable for the production of "primary" acute nephritis, for only in cases of greatest general virulence do they apparently cause nephritis, many cases of sepsis being fatal without causing nephritis.

The majority of the 91 cases classified as septic or infective were either broncho-pneumonias (with a few other pulmonary conditions) or general peritonitis originating from the genito-urinary or gastro-intestinal tracts, and it is noteworthy that neither of these two large groups gave rise to any case of acute nephritis. The former group were mainly terminal infections, which killed the enfeebled individuals without necessarily attaining any high degree of virulence. The latter (general peritonitis) were on the other hand very severe infections, often rapidly killing individuals who had been strong and healthy only a few days before. Here, apparently, we may legitimately wonder whether the typical bacteriology of "acute abdomens", with its predominantly coliform basis, is not unsuitable for the selective production of nephritis.

If we add to these groups cases of primary genito-urinary suppuration, and various abdominal

conditions whose bacteriology is that associated with the gastro-intestinal tract (cholecystitis, appenidcular abscess, portal pyaemia from appendix), we find a total of 62 out of the 91 cases in which none of the 4 cases of acute nephritis occurs.

This large group comprises chiefly conditions where either B. coli, or faecal streptococcci to a lesser extent, are responsible, along with a number of "terminal" infections (broncho-pneumonias).

Taking now the 4 verified cases of acute nephritis, they comprise,

1. One of ulcerative endocarditis of the aortic valve, superimposed on old mitral and aortic disease (male aet. 17 years). The causal organism was not isolated, but the type of endocarditis was that usually associated with a streptococcus.

2. A case of general peritonitis following pregnancy. Haemolytic streptococci were isolated from this patient's blood during life.

3. A case of septicaemia, arising from a wound of the left ankle. Streptococci were isolated from the blood in this case also during life.

4. An ethmoidal sinusitis followed by a suppurative meningitis, the lesions giving a pure culture of streptococcus haemolyticus.

Surely it is possible to conclude that the streptococcus is the organism most liable to give rise to acute nephritis. Certainly 3, and probably all 4 of the cases where it did originate were cases of pure streptococcal septicaemia. On the other hand, a large group of cases of focal sepsis, whose bacteriology was that of the gastro-intestinal tract, and therefore probably largely coliform, did not give rise to a single case. A study of the actual table given below will give the impression that ve ry few of the total cases are likely to have been pure streptococcal septicaemias, yet in four instances where this was actually or probably the case, acute nephritis arose.

Sepsis or Infection.	No. of Cases	Renal Changes.						
		Acute Nephritis.	Pyaemic Abscesses.	Infarcts.	Ascending Nephritis.	Congestion.	Toxic Changes.	No Change.
1. General Periton. of Gastro-intestinal origin.	26.	0.	1.	0.	0.	3.	14.	8.
2. Terminal broncho-pneumonia, septic broncho-pneumonia, gangrene of lungs.	20.	0.	0.	0.	0.	5.	3.	12.
3. Portal pyaemia (3 cases), appendicular abscess, genito-urinary suppuration, general periton. of genito-urinary origin, cholecystitis.	16.	0.	0.	0.	9.	0.	4.	3.
4. Lobar pneumonia	4.	0.	0.	0.	0.	2.	2.	0.
5. Bronchiectasis	1.	0.	0.	0.	0.	0.	1.	0.
6. Empyema	2.	0.	0.	0.	0.	0.	1.	1.
7. Pyaemia (two definitely staphylococcal).	4.	0.	3.	0.	0.	0.	1.	0.
8. Wound (staphylococcal)	1.	0.	0.	0.	0.	0.	0.	1.
9. Suppuration of bone.	2.	0.	0.	0.	0.	0.	1.	1.
10. Gangrene of limb.	1.	0.	0.	0.	0.	1.	0.	0.
11. Various forms of recent Endocarditis.	7.	1.	0.	3.	0.	0.	1.	2.
12. Streptococcal septicaemia from wound of ankle.	1.	1.	0.	0.	0.	0.	0.	0.

Sepsis or Infection.	No. of Cases	Renal Changes.						
		Acute Nephritis.	Pyaemic Abscesses.	Infarcts.	Ascending Nephritis.	"Congestion."	"Toxic" Changes.	No Change.
13. Meningitis, (a) middle ear, (b) ethmoidal sinus.	4.	0.	0.	0.	0.	3.	0.	1.
(haemolytic streptococcus in blood).	1.	1.	0.	0.	0.	0.	0.	0.
14. General peritonitis following labour; haemolytic streptococci in blood.	1.	1.	0.	0.	0.	0.	0.	0.

Quite a large proportion of the various forms of sepsis which failed to give rise to acute nehpritis did cause some toxic change in the kidneys short of nephritis. These toxic changes may be summarised as showing very little glomerular alterations beyond congestion, very little interstitial infiltration if any, but sometimes pretty marked cloudy and fatty changes in the tubules (or the former alone) with little or no catarrh; there is often, however, some granular albuminous material in the lumen of the tubules. They are degenerative rather than inflammatory.

In four cases which did not show acute non-suppurative nephritis, there were more than toxic changes. There were actually pyaemic abscesses in the kidneys. This would again suggest that something more specific is required for the production of acute non-suppurative nephritis that a mere bacterial bombardment of a certain degree of activity. There is evidently a distinct possibility of toxic changes being succeeded, if the infection be sufficiently severe, by foci of suppuration in the kidneys without the production of ordinary acute nephritis. We suggest that this hints that there exists a number of organisms which cannot, without local multiplication in the kidneys, give rise to changes in these organs of a severity sufficient to justify the name acute nephritis. One can conceive that the specific quality required of a nephritis-producing organism is the production of a specially large amount of exotoxin and particularly of endotoxin. Other organisms would require to live and multiply locally to produce severe renal changes, and would then naturally tend to produce pyaemic abscesses in the kidneys rather than acute non-suppurative nephritis. The organism with a large amount or virulent quality of endotoxin might be less virulent generally speaking, but in the very process of death by lysis, in the glomerular traps, might produce sufficient toxin to cause acute nephritis. Similarly, the larger the amount of exotoxin, the greater the possible damage before virulence sufficient to allow of local multiplication is established, and the greater the likelihood therefore of acute non-suppurative nephritis rather than suppurative nephritis.

In this and other sections of the thesis, we are conscious that inferences are being drawn from a comparatively small number of cases, but we believe that the basis of argument could in these cases be broadened to include much larger series without affecting the nature of the conclusions. For example,

the points we have emphasised in this series of 171 post-mortems are, we believe, merely illustrative of the type of conclusion which is generally arrived at by pathologists, and the lack of confirmatory evidence in the literature is mainly due to the paucity of attempts to approach the problem of nephritis from this particular narrow angle. It was already one's opinion, when the routine investigation of post-mortems for the above purpose was begun, that the septic cases which were associated with acute nephritis were usually streptococcal, and that many other types of infection might go on to renal suppuration before typical acute nephritis in the ordinary sense was produced. This opinion was based on the findings in post-mortems in 1925, and it was only to get a complete series of cases adequately studied from this point of view that a fresh start was made in 1926.

Only small progress can be achieved by a study of such statistics as have just been reviewed, and consequently an attempt was made to study the problem from a slightly different standpoint by making use of the clinical records of the Royal Infirmary, Aberdeen, and of similar material in the Royal Hospital for Sick Children, Aberdeen.

Our purpose was chiefly to discover if there was any evidence relating nephritis to infection, particularly to focal infection, and to find if there was any special relation to any particular kind of infection.

The records of the Royal Infirmary cases were found to be of little value from our point of view. Neither in nephritis nor in non-nephritics was the incidence or duration of focal sepsis adequately reflected in the records. A few cases personally examined showed a very high incidence of focal sepsis both in nephritics and non-nephritics, but there was neither time nor opportunity to deal with a series sufficiently extensive to be worthy of analysis.

The records and personally examined cases from the Royal Hospital for Sick Children were much more interesting for our present purpose. This would appear to be partly because it is much more frequently possible in children to obtain evidence of a sequence of events relating the nephritis to some particular cause. Such investigations of adults as have been recorded in the literature (which we will summarise later) have been evidently hampered by the frequency of focal sepsis in non-nephritics, and by the absence in nephritics of any definite evidence that the focal sepsis present is causally related to the nephritis. All too often the investigation in adults resolves itself into a proof of the coexistence of focal sepsis and nephritis, a coexistence which naturally becomes, as age advances, of ever decreasing value as an explanation of the problem.

We shall now set out the details of the investigation of nephritic children in the Sick Children's Hospital.

Children with Nephritis in the Royal Hospital for Sick Children, Aberdeen.

The period covered by the cases is from 1919 to 1926, both years inclusive, and all cases of nephritis admitted during the period are included.

The total number of cases is 51, Of these, 42 are cases of acute and 9 of subacute or chronic nephritis. All are genuine cases of nephritis, none are simply febrile or orthostatic albuminuria, etc.

The cases admitted in 1926, and some in 1925, were personally studied. Details of the earlier cases were obtained from the case records. In these, the majority of the cases, no special search had been made for septic foci etc. and only the ordinary routine examination and history were available. A few case records were obviously incomplete, but were included as negative in respect of focal infection.

Two degrees of positive finding have been distinguished.

1. Where there was coexistent focal sepsis etc. - indicated by * after the abstract of the case.

2. Where there was in addition special confirmatory evidence of relationship of the focal sepsis present to the nephritis - e.g. a clear time relationship between onset or marked exacerbation of the focal sepsis and the onset of nephritis; or an exacerbation or recurrence of the nephritis on operative interference with the focal sepsis (the importance of such evidence as indicating a causal nature for the relationship has been emphasised by Kolmer [3]).

Included in this group are cases where an acute nephritis immediately followed an acute general infection (usually scarlet fever). Cases regarded as belonging to this group are indicated by the mark **.

ACUTE NEPHRITIS.

Case 1. R.S. Male, aet. 5.

Sore throat and acute nephritis, the symptoms of the former appearing earlier by two days. The tonsils and adenoids were enlarged and filthy and not till they were removed did the nephritis clear up, which it then did rapidly. Before this, there was a period of exacerbation accompanied by the development of a pustular rash on the face.

Blood culture during exacerbation (six days incubation of broth. The blood was transferred to warmed sterile broth at the bedside and incubated immediately. 4 c.c. of blood were added to 150 c.c. of broth):- Streptococcus viridans.

Urine culture during exacerbation:- Streptococcus viridans.

**

Case 2. E.S. Fem. aet. 7.

Was suffering from a sore throat and had very large septic tonsils and adenoids. Doctor arranged for admission to the surgical wards for their removal. Next day he'phoned that he was sending her instead to a medical ward as she had just developed haematuria. On admission acute nephritis was diagnosed.

Results of laboratory investigation:-
Swab tonsils:- numerous micrococci catarrhalis, staphylococci.
Catheter urine:- a few staphylococci.
Blood culture:- negative.

Improved on removal of tonsils and adenoids, nephritis disappearing, but developed a broncho-pneumonia eight days afterwards, and eventually died.

**

Case 3. L.G.A. Male, aet. 11 yrs. 6 mos.

Sent in as an appendix case but, as symptoms were indefinite, and as he had definite asthma, he was transferred to the medical wards. During a stay of three weeks there was no evidence of nephritis; but then, while still in the ward, he developed acute appendicitis and acute nephritis on

the same day. At operation, the appendix was kinked, turgid and congested, and distended with streptococcal pus. There was some cicatrisation of the wall at the base. Subsequently the nephritis cleared up fairly rapidly. In this case the lighting up of a streptococcal appendical focus almost certainly caused the nephritis.

**

Case 4. A.F.D. Fem. aet. 8 years 9 mos.

Scarlet fever commenced 54 days before onset of present illness, and ran a satisfactory course to apparently complete cure. The tonsils on admission were enlarged, with large pus-containing crypts and faucial injection. Teeth carious. Nephritis was diagnosed and a trace of albumen was still evident in the urine on discharge.

*

Case 5. J.J. Male. aet. 5.

For 3 weeks before the nephritis started, this patient had a bad cold and inflamed tonsils with sore throat. The nephritis started with a rigor. Had had acute tonsillitis 18 months previously. The tonsils on admission were large, baggy and contained pus. In a swab from them, one found gram negative diplococci, pneumococci and non-haemolytic streptococci.

(The Dick test was negative on admission, but 11 days later the site of the old test showed a positive reaction and a scarlètiniform rash appeared, which desquamated and disappeared the next day.)

The nephritis subsided coincidently with the improvement in the tonsillar condition.
Conclusion:- Tonsillectomy and no recurrence of nephritis.

**

Case 6. V.B. Fem. aet. 3 yrs. 9 mos.

Tonsils enlarged. Nasal discharge and sore throat on admission for acute nephritis. Swab from posterior nares showed numerous diphtheroids, some pneumococci and streptococci, a few bacilli like b. influenzae.

*

Case 7. A.B. Fem. aet. 1 yr. 7 mos.
On admission tonsils were enlarged and dirty, with large crypts. Considerable amount of adenoid tissue. Rash on lips and cheek. The urine cleared completely, together with all symptoms and signs of nephritis. Then removal of the tonsils and adenoids was undertaken. The operation caused an immediate flare-up of the nephritis, with blood and casts in the urine. Condition had not completely cleared on discharge.

**

Case 8. A.N. Fem. aet. 4.
Tonsils enlarged, dirty, with muco-purulent coating. Adenoids "almost certain". Upper incisors decayed. Removal from hospital against medical advice; scanty case history and examination.

*

Case 9. P.G. Fem. aet. 5.
Admitted to surgical ward for operation for "abscess of neck". While in the ward developed acute nephritis (haematuria; epithelial, hyaline and granular casts.) Tonsils much inflamed throughout illness. Abscess opened but tonsils not removed. Abscess regarded by surgeon as tuberculosis, with possible mixed infection from the throat.
Albumen positive on last examination of urine before discharge.
Catheter urine:- no pus cells: a few gram positive bacilli, a few gram positive diplococci, and a few gram negative bacilli.

**

Case 10. I.H. Fem. aet. 2 yrs. 7 mos.
A colitis with mucus and blood in the stools immediately preceded the nephritis. Scanty case examination. Complete recovery.

**

Case 11. M.W. Fem. aet. 5 yrs. 7 mos.
Both tonsillar glands enlarged. Bacilli noted in non-catheter urine. Relieved, but casts in urine on last examination.

Case 12. J.T. Male. aet. 2 yrs. 4 mos.
Catheter urine sterile. Albumen positive on last examination before discharge.

Case 13. J.M. Male. aet. 3.

Impetigo-like eruption on face and head and here and there over the body. Some of the lesions were described as boils, and soon an abscess developed at the back of the neck. The tonsils were enlarged, the adenoids probably so. The glands in the posterior triangle were enlarged, probably from scalp infection.

The nephritis developed suddenly when the abscess and other lesions were at their height. It and the skin lesions cleared up concurrently. (Albumen positive in urine up to time of evacuation of abscess: persistently negative thereafter.)

**

Case 14. B.A. Fem. aet. 5.

Tonsils both enlarged. Two teeth decayed. Transferred to City Hospital because diphtheria developed. Six weeks after onset of illness. Had not previously had diphtheria.

*

Case 15. C.B. Fem. aet. 10 yrs. 6 mos.

Tonsils and adenoids enlarged and inflamed.

*

Case 16. D.G.L. Male. aet. 5 yrs. 1 month.

Small abscess finger developing during stay in hospital but not until 10 days after onset of nephritis.

Case 17. M.G. Fem. aet. 5 yrs. 9 mos.

Scarlet fever two years before. 12 days before nephritis right ear began to discharge: feverish: continued thus till nephritis started, when discharge diminished. (Nephritis from increased septic absorption consequent on interference with free discharge?).

Recovered from the nephritis.

**

Case 18. M.J. Fem. aet. 6.

Started with "cold". Has had profuse vaginal discharge for a year. Heavily infested with worms. Tonsils enlarged. Slight enlargement of glands at side of neck.

*

Case 19. G.R. Male. aet. 5.
Slight pain in one ear at onset of nephritis. but nil abnormal noted in ear on later examination.

Case 20. W.P. Male. aet. 11.
Tonsils have been removed for infection and enlargement. Date not stated.

*

Case 21. A.B. Male. aet. 10.
Tonsils enlarged. Evidence of disappearing herpes on abdomen.

*

Case 22. E.G. Fem. aet. 9.
Peeling of feet and history of peeling of hands. Presumed to be scarlet fever and transferred to City Hospital.

**

Case 23. N.W. Fem. aet. 9 yrs. 8 mos.
Empyema one year ago. Still evidence chest dullness etc. Tonsils both slightly enlarged. Adenoids doubtful. A few carious teeth both jaws.

*

Case 24. A.N. Male. aet. 5.
Temperature 100° on admission. No details of examination.

Case 25. W.S. Male. aet. 9 mos.
Stools very loose. History of Coryza before onset. Examination very incomplete.
Result:- death.

*

Case 26. J.W. Male. aet. 4 yrs. 10 mos.
Diarrhoea before onset of acute nephritis, which was sudden.
Result:- death.

*

Case 27. H.S. Male. aet. 7.
Became very ill with Ludwig's angina: oedema of larynx: cervical glands much enlarged: large abscess left side of neck.
Impetigo for a fortnight before.
Temperature 103.5° on admission.
Sudden development of acute nephritis whilst abscess was at its height. Operation - evacuation of thin "streptococcal-like pus" (microscopically - streptococci). Nephritis improved after operation but after a week had not completely cleared, and temperature remained elevated. The original incision was then extended, and the temperature immediately came down; the albuminuria, oedema, etc. soon completely disappeared.

**

Case 28. J.M. Male. aet. 10.
B. coli in non-catheter urine. Had swinging temperature at times (up to 102.5°) focus not discovered.

?*

Case 29. W.G. Male. aet. 10.
Influenza 2 weeks before; recovery not complete; eyes became sore - conjunctivitis; sudden onset of acute nephritis.

**

Case 30. M.A.C. Fem. aet. 11.
Rheumatic fever 7 years ago. On the day before the nephritis started, the mother states that the head"broke out". Simultaneously with the nephritis, pain started in the joints. (Heart, examined in ward, showed systolic mitral murmur and accentuated second sounds; slightly enlarged.) Embolic nephritis ?

**

Case 31. R.P. Male. aet. 6.
Temperature 100° on admission. Incomplete history and no record of examination.

Case 32. A.B. Fem. aet. 11.
History of very sore throat a month ago; later pains in back, sides and legs, which persisted. Fortnight ago acute nephritis started. Sore throat

was still marked but had gone before admission; enlarged septic tonsils were present, however.

**

Case 33. A.B. Male. aet. 4.
19 days before onset of nephritis had a bad cold and shivering. Stools slimy but bowels regular: persisted till admission; admitted 2 days after the onset of acute nephritis. Temperature 103°.
Temperature remained high for a week.
No detailed examination recorded.

**

Case 34. W.D. Male. aet. 6.
Discharge from left ear on admission.
Mastoid disease confirmed in hospital.
Inflammation of left conjunctiva while in hospital.
Condition of tonsils and adenoids not noted.

*

Case 35. M.M. Fem. aet. 5.
History of a "chill" a fortnight ago.
A week ago sore throat, feverish, and glands in neck swollen. About same time mother noticed oedema under the eyes, and headache.
On admission definite acute nephritis.
Tonsils enlarged and septic.

**

Case 36. F.E. Male. aet. 11 yrs. 9 mos.
Mother says got a "chill at the baths" 2-3 months ago. This was followed by dulness of hearing which cleared up eventually.
Fortnight ago - headache, oedema, etc. - acute nephritis.
No record of examination after admission, save of kidneys and urine.

Case 37. W.H. Male. aet. 6 yrs. 5 mos.
No recorded focal sepsis or cause.

Case 38. I.D. Fem. aet. 3 yrs. 6 mos.
Purpuric spots on back immediately preceded nephritis. Similar attack one year ago, with the purpura more prominent, and the nephritis slight.
No record of throat examination.

*

Case 39. R.S. Male. aet. 4 yrs. 6 mos.
Tonsils rather inlfamed and are enlarged.
Several teeth decayed.

*

Case 40. A.G. Fem. aet. 6.
History of "influenza" 4 weeks ago and apparent recovery. 5 days ago sickness and vomiting, recurring 3 days ago.
? convulsions: swelling of face and blood in urine (Dr.)
No note of throat appearances.
Desquamation of feet and legs, and skin rather dry.
Considered to be Post-Scarlatinal nephritis.

**

Case 41. A.S. Fem. aet. 7 yrs. 6 mos.
Illness began with vague pains and anorexia. Later vomiting and signs of acute nephritis.
Temperature 102° on admission.

?*

Case 42. R.I. Male. aet. 6,
Illness started with eruption on head.
Foetid stools.
Later headache, and, still later, progressive oedema.

**

SUMMARY.

Focal sepsis, or acute disease, apparently related to the nephritis, was found in 34 out of 42 cases of acute nephritis (81%).

Of the remaining cases, several are cases with little or no record of examination in the case sheet, which consists practically of a brief history on admission.

In 16 of the 34 cases, there was evidence of varying character which greatly strengthened the impression of relationship between the infection and the nephritis.

Control observations were made in 50 consecutive full case records of children in the wards suffering from nervous diseases. They did not show any comparable incidence (only in 14 out of 50 cases - 28%). Where present, focal sepsis was present in 13 of the 14 cases in tonsils or adenoids or both. In the remaining case a blepharitis was recorded. Usually the tonsillar or adenoid condition was slight. The nervous system was selected, as, upon the whole, there is little suggestion in its diseases of special focal sepsis or, of course, of special freedom from it. Access to complete records of apparently healthy children was not available. In making out the control series consecutive cases were taken, with the exception that all incompletely taken cases were omitted,- so that the incidence of focal sepsis found is presumably nearly a true one, and higher than that of a series strictly comparable to the nephritic one i.e. higher than a series including incomplete records.

It may be asked why 50 consecutive (complete) cases of all diseases (excluding nephritis) were not taken. Such a series was contemplated, but it soon became obvious that the incidence of focal sepsis showed significant relation, not only to nephritis, but to a number of other diseases (rheumatic fever etc.) It was therefore clear that by such a comparison we would be attempting to contrast the incidence of focal sepsis in

nephritis with its incidence in a group of cases containing a large number of examples of one or two common conditions, in which also there was a special relationship.

(This "all diseases" series was eventually completed, and, although we do no think it as proper a control standard as the previously quoted one, it showed a 42% incidence of focal sepsis in a series of 50 cases; all of the 5 cases of rheumatic fever included showed focal-tonsillar-sepsis, as naturally did other 5 admitted for "tonsils and adenoids".)

Bacteriology.

Evidence suggesting the organism at work was found in 9 cases (Nos. 3,1,5,6,9,22,27,28,40.)

One of these showed b. coli (catheter urine) (No. 28.)

Five showed streptococci alone (including as streptococcal 2 cases of scarletinal nephritis, the other three being respectively a streptococcal septicaemia, an appendicitis and a neck abscess, (Nos. 1,3,22,27,40.)

In one a throat swab showed gram negative diplococci, pneumococci, and non-haemolytic streptococci (No. 5).

In one a throat swab showed gram negative diplococci, numerous diphtheroids, some pneumococci and streptococci: a few bacilli like influenza bacilli (No. 6).

In one, gram positive diplococci, gram positive and gram negative bacilli were found in the catheter urine (no pus cells) (No. 9).

Thus, 7 of the 9 in which some observation of the bacteriology had been made showed streptococci; it would be safer to ignore the two throat swabs, in view of the varied bacteriology (including streptococci) of the throat in health. This gives an incidence of streptococci in 5 of 7 cases.

Evidence of the presence of focal sepsis or of apparently related acute infection is recorded in cases No. 1,2,3,4,5,6,7,8,9,10,13,14,15,17,18, 20,21,22,23,25,26,27,28,29,30,32,33,34,35,38,39, 40,41,42,(34 cases).

Of these, the 16 in which there is some special evidence to prove the relationship to nephritis are Nos. 1,2,3,5,7,9,13,17,22,27,29,30,32,35,40,42.

The 8 cases without recorded focal sepsis are Nos. 11,12,16,19,24,31,36,37,41.

Table showing Sites of Focal Sepsis (or name of related infection).

A number of cases showed several foci, but only the most prominent in each case is recorded.

Site of Focal Sepsis or name of related infection.	Total No. of Cases.	Reference Nos. of Cases.
Integumentary System.	2	13,42.
Ludwig's angina.	1	27.
Throat (tonsils,adenoids).	17	1,2,4,5,6,7,8,9, 14,15,18,20,21, 23,32,35,39.
Ears.	2	17,34.
Appendix.	1	3.
Colitis etc.	4	10,25?,26,33.
Influenza ?	1	29.
Rheumatic fever	1	30.
Scarlet fever	2	22,40.
Purpura	1	38.
Vague	2	41,28.(b. coli in catheter urine).

SUBACUTE AND CHRONIC NEPHRITIS.

Case 1. J.H. Male. aet. 8.
Subacute nephritis. Showed dry scars of old posterior perforation in both ears; while in hospital developed streptococcal pleural effusion, going on to empyema, which was drained.

*

Case 2. M.M. Fem. aet. 6.
Subacute nephritis, slight congestion of pharynx. Nil abnormal noted in tonsils and adenoids.

Case 3. J.G. Fem. aet. 10.
Chronic nephritis. Readmission. Scarlet fever when one year old.

Case 4. J.W. Male. aet. 9.
Chronic parenchymatous nephritis. No focal sepsis discoverable; began over 12 months before; since then always had oedema and albuminuria on repeated admissions; tendency to uraemic symptoms; bilateral decapsulation performed with resultant temporary diminution of oedema. (Kidneys at operation were large and pale, with capsules stripping very easily). Discharged in statu quo.
These details are irrelevant to the present issue, but they serve to indicate how a long continued nephritis, with copious albuminuria and marked oedema, (but no R.B.C's.) may not, in over a year, cause any contraction of the kidney.

Case 5. D.K. Male. aet. 2 yrs. 1 month.
Chronic nephritis. Tonsils moderately enlarged and a fair amount of adenoid tissue. Has had condition for a year. First symptom dyspnoea, and indeed intermittent dyspnoea was the chief complaint throughout the year, though had swelling under the eyes intermittently.
(A short note adds that a week after discharge from the Sick Children's Hospital, he was admitted to the City Hospital, and in another week died of uraemia. The stated cause for admission to the City Hospital was "dyspnoea". Post-mortem, no cause for the dyspnoea was found in the air passages, and it is said that an"acute glomerular nephritis" was found with very marked suprarenal haemorrhages.)

*

Case 6. C.S. Fem. aet. 11.

Chronic nephritis. Had very bad purpura for four months (2 years ago). Ever since has had difficulty in walking and puffiness under the eyes; on slightest chill, headaches and vomiting, etc.; tonsils and adenoids - no note of examination.

**

Case 7. J.M. Male. aet. 9.

Scarlet fever 5 years ago and no definite history of nephritis thereafter; but mother said has been "puffy" ever since. Admitted for marked oedema and albuminuria.

**

Case 8. L.C. Fem. aet. 10.

Chronic nephritis. Scarlet fever 5 years ago was followed by nephritis with which the child was in hospital for 3 weeks. Never right since. Present attack succeeded an attack of severe conjunctivitis.

(Readmitted subsequently, a year later - 1921; had been ill all intervening time; sore throat while in hospital.)

**

Case 9. V.S.P. Male. aet. 11.

"Chronic interstitial nephritis with superadded acute phase". Minor uraemic symptoms. Has had condition since aged 3. Present exacerbation followed directly on an attack of German measles.

No record of clinical examination save of kidneys.

SUMMARY.

Five of the 9 cases have recorded evidence of cause (Nos. 1,5,6,7 and 8). In two of these the origin was in an attack of scarlet fever, in another in an Otitis media, followed by empyema and apparently streptococcal. In the others no hint of the causal organism was obtained.

CONCLUSIONS.

The great majority (81%) of cases of acute nephritis in children showed discoverable focal sepsis or relation to acute infection. It is highly probable that the relationships found were causal, as controls, (other patients in the same ward) showed nothing like an equivalent percentage with focal sepsis.

In a remarkable number of the cases (16), more than the mere presence of the focal sepsis etc. was indicated by the record. There was evidence directly linking the sepsis present to the nephritis.

A number of the records in which no focal sepsis was noted were obviously incomplete in other respects.

Focal sepsis or evidence of causation was obtained in 5 out of 9 cases of subacute or chronic nephritis. These cases were admitted long after the onset, which was usually fairly acute, and naturally a greater difficulty in ascertaining the original cause was to be anticipated.

We think it is justifiable to conclude that these cases form strong evidence that, in children at least, a careful examination can usually, if not invariably, furnish evidence, not only of an infective origin for nephritis, but even of the original locus of the infection.

If focal sepsis takes such a leading role in the production of acute and other nephritis as it appears to do in these cases, it becomes obviously the most important part of the treatment to deal with such foci. This is the more evident since we see fairly constantly in the individual case records a distinct corelation between subsidence of the initial infection and disappearance of the nephritis. This is the case whether the initial infection e.g. a tonsillitis has subsided under treatment or more or less spontaneously. Indeed, if we go by these case records, it is scarcely too much to believe that the only important results of treatment of acute nephritis are the action of the treatment upon the primary focus, and that the nephritis which is "cured" is the nephritis in which, as a result of (or, as often coincidently with) treatment, this original focus disappears; and

that the uncured cases, those which drag on and become chronic, are those in which infection persists, in an untreated focus, an inadequately treated focus, or in an undiscovered focus.

It would seem on general grounds quite unjustifiable to believe that in any case, or at least in any appreciable number of cases, the initial renal damage is such as, on complete removal of the causal infection elsewhere in the body, the damage already done is sufficient to render inevitable any considerable degree of permanent renal insufficiency, or even of recognisable anatomical change. Certainly, as we shall see in Section 2 of this thesis, there are no experimental grounds for such an assumption. Even were such a thing possible, it is not fair or reasonable to allow such a supposition to influence treatment. Until it can be shown definitely that little or no part of the chronicity in chronic cases is dependent upon persistence of focal infection, it is quite unjustifiable to place the hunt for, and attempted eradication of, such sepsis in the background. The prognosis of acute nephritis, in children especially, has long been known to depend very largely on the early or late start of treatment (Smellie, 156). Is it not possible that the main therapeutic value of such early treatment depends largely upon the effect of the rest included in it in permitting of a conquest of the causal sepsis? We will elaborate later the view that nephritis is caused by a bombardment of the kidneys with organisms and their toxins, usually with streptococci. the organisms being in part excreted, in part lysed in the glomeruli with production of endotoxin, and that there is no bacterial focus in the ordinary sense of the word in the kidneys themselves. On such a view, progressive damage is very much less likely if the septic focus elsewhere from which the organisms and toxin are being constantly derived is eradicated.

Even the undoubted occasional occurrence of progressive nephritis after scarlet fever does not necessarily negative this view. Cases 7 and 8 of our "subacute or chronic" series are of this type. (That such a progression of post-scarletinal nephritis may occur cannot be doubted, though it has been challenged e.g. by Leichenstein, by Bull and by Bartels - quoted by Teissier and Duvoir(160). Teissier and Duvoir themselves, however, are strongly of opinion that, though it is not

common, chronic nephritis can occur as a sequel of scarlet fever, and they quote Potain, Puot, Brault, Cornil and Ranvier, and Castaigne as agreeing with this view.) Such rare cases may surely be due to an abnormal persistence of scarletinal streptococci in some focus in the body (e.g. tonsils, middle ear, etc.), and need not necessarily be secondary "healing" changes from a past acute infection.

Returning to the question of the aetiology of acute nephritis we have found infective origin so frequently inferable in these children, that it is probable that the remaining few are explained in a similar manner by an infection at a less obvious primary site. We do not mean in dealing with these acute cases that necessarily a septic focus has been present for some time before the onset of nephritis. This has probably been the case in some instances, but what we do believe to be invariable is, first, that the process is an infection (probably usually streptococcal), and, secondly, that the active damage to the kidneys continues only so long as there is a toxaemia, sometimes accompanied by a low grade septicaemia. We do not believe that it is a case of infection arriving in the blood with minimal or no changes at the point of entry and "settling down" in the kidney. A brief septicaemia of suitable bacteriology will, without any necessary "focus" at the point of entry or elsewhere, cause a brief but possibly severe or even fatal acute nephritis. Bacteriaemia and toxaemia without localisation is, however, of very brief duration in man, and the active damage to the kidneys ends when the septicaemia and toxaemia are overcome. A more prolonged action of toxins and of showers of bacteria in the blood is secured where there is a focus from which such organisms and toxins may be distributed and this is the more usual source of acute nephritis, and probably the only source of a prolonged or chronic nephritis.

It is not easy to say definitely why a connection with focal sepsis is more difficult to trace in adults. To overcome the difficulty by postulating a difference in cause does not seem satisfactory. It may be that in the adult also the septic process is present and causal, but not so prominent and of course chronic septic foci are not so unusual in non-nephritic subjects. In the "virgin soil" of the child's tissues, the problem is simpler, and one may regard nephritis as dependent largely on the suitability of the type of infectious process and on its passing beyond a certain critical point of severity.

In adults, the soil is no longer "virgin soil". The sepsis may have been of long standing, and the immunity reactions may be considerable. A focal exacerbation may be balanced by an adequately raised immunity. A negative phase in the immunity reactions may create a more favorable state of affairs for the development of nephritis (although there may be no markedly increased activity of the focal sepsis) than does the flagrant focal exacerbation. Similarly, the bacteriology of a long-standing focus may change at some date to one more favorable to the production of nephritis. Further, deep seated foci, more difficult to detect, may supplant the more easily detected superficial foci of earlier years: dental or tonsillar foci may have subsided, or teeth or tonsils have been removed, but not before a chronic appendicitis or other deep seated lesion has become established.

If these arguments have any weight, we can only expect to find in adult nephritics a picture consistent with an origin in focal sepsis, and not a proof of such origin in the manner we find it proved from case records in children. The one feature the "consistent" picture referred to demands is a very high, preferably an invariable, incidence of focal sepsis in nephritic cases.

We must remember, however, as far as concerns the Army statistics quoted, their method of compilation was not one which would adequately reflect the incidence of acute nephritis in such conditions as tonsillitis, etc. Even had quite a number of cases had a history such as we record in many of these children, the primary admission would probably have been put down as for "acute nephritis", and these important cases would therefore not appear in the total of, say, tonsillitis cases, or in the figures giving the incidence of complications in tonsillitis.

As to the particular type of organism found in our series of child nephritics, in only 7 of the acute cases was fairly reliable evidence found, and 5 of these (including 2 cases of scarlet fever), were streptococcal, a result which, with other evidence already indicated, and with evidence yet to be referred to, is strongly in favour of the view that streptococci are more suitably constituted for the production of nephritis than are other organisms.

It would, however, be unwise to strain the view of streptococcal selectivity too much, in an attempt to maintain that the presence in sufficiently virulent form of one group of organisms, is the sole factor at work in determining the onset of acute nephritis. It is quite possible that unfavourable influences acting on the kidneys - malpositions, chill, etc. may predispose them to acute infection, and there is also a sufficient number of recorded cases of familial nephritis (Eason and others) to indicate that a hereditary vulnerability of the kidneys may possibly exist. The extent to which we must rely on individual or hereditary variations in renal susceptibility is, however, perhaps not so great as a cursory view might indicate.

In the first place, if it be true that streptococcci and possibly some other bacteria with a s similarly powerful renal action, are much more likely than many other organisms to cause an acute nephritis, there is an obvious explanation of the absence of acute nephritis in many septic conditions where the bacteriology is unsuitable for its production. Even when thus narrowing the issue, many evidently streptococcal cases of sepsis do not lead to nephritis. We need seek no further than scarlet fever for this. The majority of cases of scarlet fever escape without acute nephritis.

A further narrowing of the actual incidence of nephritis might, however, be quite conceivably due to variation in the amount of toxin produced. For instance, *in vitro* production of toxin varies greatly from strain to strain of streptococcus scarletinae, and does not necessarily vary with the severity of the cases from which the various strains were derived. Still more there may be variation in the amount and type of toxin, endo- and exo- toxin, produced by various members of the streptococcal group. We have not found evidence which justifies us in allotting a nephritis producing power to any particular group or groups of streptococcci, but it is on the face of it unlikely that all are identical in this respect. In scarlet fever and probably in other streptococcal infections, we have probably to deal in addition with the operation of the rather complex factors which lead up to anaphylactic susceptibility, and it may therefore be that factors of time of infection, completeness of remission, and suddenness and time of reactivity, all play a part in determining whether, even with a given kidney and a given strain of streptococcus, nephritis will develop.

Our next task is to review the literature dealing with the clinical investigation of nephritis.

An investigation of the literature of this aspect of our problem shows it to be scattered and somewhat scanty. Although inadequate, it does, however, present one or two features which are worthy of note.

The procedure adopted by investigators has usually been to examine the urine or blood of nephritis, or, in some cases, of both. Sometimes, too, focal sepsis has been recorded, due to the same organism as was recovered in the blood or urine.

It was evident from the start that all observers had claimed a higher percentage of positive bacterial findings in the urine than they did in the blood where the latter was examined. Although other factors may have been at work in producing this result, it immediately suggested the possibility of fallacy in the urinary findings.

To begin with, therefore, it was necessary to determine whether it was invariable, or almost so, to find the catheter urine free from bacteria in (a) non-nephritics with other diseases, and in (b) healthy subjects.

(a) Urine in non-nephritics with other diseases.

In this group of individuals "suffering from other diseases it is obvious that nephritis, at least in the sense of Bright's disease, is not essential to the excretion of organisms in the urine. Excretion of bacteria in disease other than nephritis is common, particularly in acute conditions (anthrax, chicken cholera, hog cholera, glanders, Malta fever, plague, relapsing fever?, swine erysipelas, tuberculosis, typhoid and paratyphoid, in some pneumonias, and, according to some, in leprosy). Influenza bacilli have also been found in the urine (Raskay 140). Conradi and Bierast (28) report the presence even of diphtheria bacilli in the urine of 53 out of 155 cases of diphtheria. McCrae (96) gives the figures for typhoid as from 20% - 25%.

Dick and Dick (38) found streptococci in the urine in a number of cases of scarlet fever, and they quote Tunnicliff as having made a similar observation in 28 out of 50 cases of the same disease.

Turning to chronic conditions, focal infections are prominently associated with bacteriuria. This has been emphasised by a number of observers. Dick and Dick

(38), report 5 cases with chronic septic foci in all of which bacteria were found in the urine (streptococci in 4). Kirk (77) reports similarly positive results.

In a number of chronic conditions which are also probably due to focal sepsis (e.g. rheumatoid arthritis etc.) bacteriuria is common. Further, it is common in chronic constipation. (Chalmers Watson and others.)

Is the kidney which excretes these organisms itself healthy, or is excreting possible only when some degree of damage has occurred? Various answers have been given to these questions. Some writers practically include the excreting of organisms amongst the essential functions of the kidney, and seem to regard the healthy organ as possessing the power to do so. There is no doubt that the excretion occurs usually without clinically detectable renal involvement, and that even post-mortem examination reveals no prominent lesion. In spite of this, however, a minimal degree of damage may have been inflicted by the organisms in their passage. Writing on this point, Kanjajeff (71) says that post-mortem examination of clinically normal kidneys from cases of typhoid fever with typhoid bacilli in the urine, shows that none are really normal. All show small foci of necrosis under the capsule. Wyssokowitsch (174) injected large numbers of bacilli intravenously in animals, and never found them in the urine without microscopic evidence of damage to the kidneys.

It may therefore be taken as true that whilst sometimes no damage may be sustained by the kidney during the excretion of organisms, yet in many other cases some harm is done. Such lesions as are produced may take the form of small focal necroses, perhaps in the glomerular tufts chiefly, of which the permanent residuum may be at most a minute scar.

Briefly, then, bacteriuria may be due either to acute or chronic infection, and is a phenomenon of very widespread occurrence. Moreover, the fact that in many common chronic infections there is the possibility of a bacterial bombardment of the kidneys, probably not a constant one, but nevertheless intermittently sustained over years, taken with the further fact that there is evidence that such bacterial emboli may, without detectable clinical signs at the time, insidiously injure the kidneys, provides a very feasible basis for the origin of those cases of chronic nephritis which develop without there having been at any time manifestations of acute or subacute nephritis.

We shall leave here the bacteriology of the urine in diseases other than nephritis, adopting one obvious lesson from the fact - namely, that if bacteriuria be found frequently in cases of nephritis, particularly in chronic nephritis, this is to be regarded chiefly as indicating indirectly that a primary lesion exists somewhere in the body. This primary lesion (in chronic cases probably a chronic septic focus) is responsible for the bacteriuria, and, probably for the nephritis, if the association be frequent enough to justify this statement. In other words the incidence of bacteriuria apart from nephritis does not render its investigation in nephritis futile, but it clearly shows that the demonstration of bacteriuria is useful simply as an indirect indication of the presence of focal sepsis, which may from other points of view have escaped attention.

(b) Urine in healthy subjects.

A preliminary investigation of this problem also is necessary. Is it invariable, under the usual conditions of catheterisation etc. for the urine of a healthy subject to be sterile?

D.J. Davis (36) found the urine sterile in 38 out of 43 normal individuals. Of the remainder, 3 contained b. coli (one also showing in the sediment a gram negative coccus which could not be cultivated) and 2 showed gram positive diphtheroids (probably from contamination by prepucial sebum J.G.)

Pfeiffer (133) found pseudo-diphtheria bacilli in 84% of normal urines examined.

Oldmachar (115) found pseudo-diphtheria bacilli in 12% of 80 cases examined.

Kolle and Wassermann (82) state that staphylococcus aureus and albus are normal inhabitants of the anterior urethra.

It is possible that the technique of these different observers, both of obtaining the catheter specimen and of subsequent cultivation, varied greatly, and so this may to a great extent explain the variation in their results, but for our present purpose of critical investigation of the literature, we must assume that a similar variation may have existed in the technique of others whose results we are about to consider in relation to nephritic cases.

The logical deduction is therefore that an organism reported in nephritis cases which is also reported with any frequency in any of these normal series, is immediately suspect, and, unless very strong reason can be advanced to the contrary, must be viewed as without any proved relation to a disease process. For the moment we need pay but little heed to diphtheroids in particular, but also possibly to staphylococci and to b. coli. The two latter are probably frequently excreted by the kidneys in patients with corresponding focal lesions; but, as we have seen, the technique used by some observers has not sufficed to exclude them from a "healthy" series.

This indirect method of estimating the trustworthiness of recorded observations on nephritics is rendered necessary by the fact that hardly any of the observers concerned tested their methods (which often included specially delicate cultural methods) on an adequate series of control cases.

Bacteriuria etc. in Chronic Nephritis.

If in spite of this more rigorous standard (of denying the proved significance of certain organisms) the urine of the chronic nephritic, with which we will deal first, is still not sterile in a fairly high percentage of cases. the contrast with the healthy urine will be striking, and an indirect clue to the frequent coexistence of focal sepsis will be obtained. The evidence will be at least consistent with the view that bacterial emboli from such septic foci are at work in the production of the nephritis. Were a similarly high percentage of positive results obtained in other diseases, a causal relationship would no doubt be claimed, and it seems then not unreasonable to claim it here, where the very presence of bacteriuria proves the passage of the organisms through the tissue concerned.

The plea that bacteriuria is frequent in other common chronic diseases loses much of its force when we recall that there is nothing to indicate that in such conditions an insidious renal damage is not proceeding. although in many cases it may never reach a degree sufficient to endanger life.

Let us then note what various observers have found.

Lustgarten and Manneberg (94) and Scheidemandel (150) repeatedly found streptococci in smears from the sedimented urine without being able to cultivate them.

Dick and Dick (37) successfully cultivated bacteria from the urine of every one of 13 cases of chronic nephritis examined. In these cases, staphylococci and pseudo-diphtheria bacilli were not regarded as positive findings. Contamination was, they think, excluded, as indicated in some cases by the discovery of a focal lesion with the same bacteriology as the urine.

Seven of the thirteen cases showed streptococci, sometimes along with other organisms, whereas the other six showed anaerobic bacilli, gram negative or gram positive. Where a focal lesion of identical bacteriology was found, it was always in streptococcal cases. This gives us rather greater assurance that the organism in these cases was a non-contaminant than in the cases showing anaerobes. Unfortunately, the Dicks record only four controls (all negative as regards organisms which they consider to be of importance), and seeing that few if any other observers have used their very thorough technique for anaerobic cultivation, there must be some doubt as to the significance of the anaerobes found.

Such a doubt is augmented by a paper by Reith (141) who, using the strictest aseptic precautions, found anaerobes in the muscles and blood of a large percentage of normal animals of different species.

It is interesting, in passing, to note the finding of the Dicks in a case of nephritis due to phenol poisoning. They could find staphylococcus albus only. This being one of the organisms whose significance we have shown reason to doubt, the case, so far as it goes, fails to give any support to the view that might be put forward that the nephritic kidney excretes organisms only in consequence of an altered filterability subsequent to the nephritis.

Cary (20) claims to have found organisms in all but two of twenty cases of chronic nephritis. No controls are recorded. Diphtheroids, found and held responsible in eight cases, we are excluding, also staphylococcus aureus, found in three cases (but always with other organisms).

The other cases showed

Strep. haemolyticus	1 case.	
Gram positive spore-bearers	4 cases	(in 1 case with other organisms).
Diplococcus crassus	1 case	
B. coli	2 cases	(1 case with other organisms).
Strep. viridans	3 cases	
No growth	2 cases	(of these 2, one had many haemolytic streptococci in the tonsils, and the other died from streptococcus viridans endocarditis).

Of the 20 cases, 15 are recorded as showing definite focal infection. The difficulty of controls on this point is admitted to be considerable.

Both Dick and Dick and Cary therefore obtained from the urines of chronic nephritics, organisms in an unusually high percentage of cases. On their own interpretation they obtained respectively 100% and 90% of positive results. On the stricter interpretation of their conclusions which we propose, it is unlikely that an adequate group of normal controls would have given any appreciable percentage of positive results, yet even in this interpretation both gave over 50% of positives (i.e. excluding diphtheroids, staphylococci and anaerobes). Moreover, since we are regarding the bacteriuria chiefly as indirect evidence of the presence of active disseminating septic foci, Cary's two "no growth" cases might be from this point of view added to the positive results, for one showed haemolytic streptococci in the tonsils, the other streptococcus viridans in cardiac vegetations - both almost certainly"disseminating" foci.

As already mentioned, 15 of Cary's 20 cases showed septic foci on examination.

Taking these and other observers already quoted (Lustgarten and Manneberg; Scheidemandel), it is notable how frequently streptococci in particular have been found, especially, though not exclusively, of the non-haemolytic type. This streptococcus is well known to be frequent in persistent focal lesions, and to be capable of

repeated systemic invasion. At the same time, by such invasion it does not usually produce anything of the nature of pyaemic abscesses, and it is therefore the more likely to be concerned in such an insidious condition as chronic nephritis is.

It is only with regard to organisms of low virulence and with little capacity for multiplying in metastatic foci that we are likely to make out any case at all in relation to chronic nephritis. We can scarcely admit as frequent causal agents organisms whose presence in the blood we know to be usually associated with grave acute septicaemia or pyaemic manifestations.

We conclude that focal infection, frequently streptococcal, but possibly in quite a number of cases due to other organisms, is very frequently present in chronic nephritis, and that this infection in a large number of such cases gives rise to systemic invasion and bacteriuria.

Standards which would give 100% negative findings in healthy urines, give over 50% positive findings in nephritic urines. When we consider that the observers concerned apparently examined the urine in each case on only one occasion, the percentage appears even more significant, for it is open to doubt whether a bacteriuria from a chronic focus would, when present, be constantly present.

Records of blood culture in chronic nephritis were not found in the literature. It is probable that, if made, they would be mostly negative. The numbers of bacteria in the blood at any time are probably very small, their presence intermittent, and the bactericidal power of the blood considerable.

We may with advantage at this point recall a type of patchy chronic glomerulo-nephritis of undoubted embolic origin, which bears many resemblances to chronic nephritis arising insidiously. This is the nephritis due to subacute bacterial endocarditis, generally caused by streptococcus viridans. It has been repeatedly described (Löhlein 92 Baehr 6 Warwick 167), and experimentally has been produced by Gaskell (53), Clausen (24) and Leiter (88), the last named finding the typical changes as marked with the use of mechanical particles (lycopodium spores) as of bacteria.

These experimental observations are detailed in Section 2 of this thesis (p.164). The embolic particles in this nephritis are probably larger than any which would be derived from other sources involving passage of the emboli through the lung capillaries, and consequently the larger. more scattered, areas of fibrosis resulting in the endocarditis cases are just what might be expected if the condition differed in this point only from chronic nephritis arising insidiously. While it cannot be claimed that other differences do not exist, it is possible that, such as they are, they are explicable on the basis of the less purely mechanical results produced by smaller emboli, composed more exclusively of bacteria. The bacteria probably set up some degree of inflammation in the tufts in which they are trapped and thus the histological picture is somewhat modified. Further, with the initial damage more frequently intra-glomerular, the capsular epithelium etc. may be expected to show greater reaction than if it were merely involved in a glomerular atrophy resulting from the block of an artery - whether interlobular or afferent.

Clinical Investigation of the Causation of Acute Nephritis.

In acute nephritis the investigation has sometimes included cultivation from both blood and urine.

One or two isolated results, recorded by the observers chiefly because they appeared to be of an exceptional nature, will first be noted.

Dick and Dick, in the article already referred to, found a nephritic kidney, from a case of diphtheria, to contain innumerable colonies of true diphtheria bacilli. together with a few staphylococci and streptococci.

Huebschmann (66) reports a single case of acute glomerular nephritis in meningococcus infection. He thinks it the first case on record.

Rojar and Morengo (143) record 19 cases of hookworm infestation in which acute nephritis with urea retention was present, and was cured by anthelmintic treatment. In these cases further investigation as to the cause is required. Either toxic products from worms or a secondary invader admitted at the duodenal lesions may have been responsible.

Turning to more definite attempts to probe the general etiological problem, we find that Brewer (14) made blood cultures in a number of cases of post-scarletinal nephritis, and found them negative. His technique is not given in detail. but his period of incubation of the cultures was probably inadequate.

Councilman (32) could get cultures post-mortem from kidneys in acute or subacute nephritis only when septicaemia was present.

Shaw Dunn and Thompson (152) in a paper already referred to (p. 27) found 13 undiagnosed cases of acute nephritis in 660 post-mortems. All these were cases with sepsis. In 8 cases the sepsis was due to streptococci, in one case to pneumococci and in one case to staphylococci.

Dick and Dick (37) examined the urine of 7 cases of acute nephritis. 4 showed streptococci. The other 3 showed a variety of anaerobes. We have already, in dealing with the same writers' findings in chronic nephritis, expressed an inclination to accept the streptococcal findings, and to doubt the others.

An important paper is that of Eason and Buchanan (43). In 2 of 4 cases of acute nephritis examined, these authors found non-haemolytic streptococci in both blood and urine. The organisms were of the type ordinarily saprophytic. They corresponded in all respects to types found in the teeth and tonsils of the individuals concerned (males of 18 and 19 years respectively). A noteworthy feature was the late appearance of growth on cultivation:- not till the 5th or 6th day. One of the cases was examined after the nephritis had disappeared and gave a negative result on blood culture.

These investigators were at the time chiefly concerned with the study of "familial" nephritis, but even in such cases they regard the

etiology as infective, with,however, a special hereditary susceptibility of the kidneys.

Turning to children, two observers report results which are in accord with those we have reported earlier from the Sick Children's Hospital, Aberdeen, in that a definite cause is shown to be ascertainable in a very high percentage of cases with acute nephritis. S.W. Clausen (25) found nasal sinusitis in 11 consecutive cases of acute "parenchymatous" nephritis in children; the removal of tonsils and adenoids often gave no permanent benefit, but relief,striking and often permanent, followed in every instance in which definite improvement in the nasal sinus infection could be obtained.

R.S. Allison (/) in 8 of 12 cases of acute nephritis in children found marked enlargement and chronic inflammation of the tonsils and adenoids. All these cases cleared up on removal of the inflamed tissues.

This almost concludes the list of clinical records which have been traced. Another paper is of interest, however. Campbell and Rhea (18) describe a nephritic inflammation of infective and, they believe, of haematogenous origin, which, however, we have to regard as not being the disease we are investigating - acute nephritis in the sense of acute non-suppurative Bright's disease.

They describe 13 cases in which the kidneys showed multiple small or large areas of acute infection which in most cases led to abscess formation. The majority of cases were unilateral. Of the 13, the majority were caused by b.coli, but in a few the infective agents were staphylococcus aureus or b.typhosus. (In all 13 the bacterial origin was verified at operation or post-mortem). The condition was usually amenable to surgical treatment. The disease as described is sufficiently different from the ordinary acute nephritis to justify its definite exclusion from our classification. It is fair, we think, to conclude that the difference is due to the fact that the kidney or kidneys were here the seat of metastatic multiplication of the organisms implicated, and, thus we are reminded that such a multiplication of organisms is likely to lead, not to the ordinary acute nephritis, but to this distinct condition - to pyaemic suppuration. If organisms cause acute nephritis, the method of action must be either by their toxins or by damage caused by lysis of many of the bacteria as they reach the kidneys.

An obvious bearing of this conclusion is that we cannot expect, even with an organismal cause for acute nephritis, to find organisms either constantly or abundantly in the urine, in the same way as we would in such cases as Campbell and Rhea describe.

(The origin of acute glomerulo-nephritis by the lysis of bacteria in the glomeruli is strongly upheld by Ophüls (119), in a paper to which we shall refer again later.)

What should be our conclusion from the results of these various investigations? The material is very scanty. The isolated findings of diphtheria bacilli (Dick and Dick) of meningococci (Huebschmann) along with occasional similar cases recorded in the literature, suggest that in exceptional cases, any of a number of bacteria may be justly held responsible. The paucity of such reports is, however, consistent with the conclusions we have already been tempted to draw from other standpoints. That is, they indicate that a nephritis does occasionally occur in severe acute infections of many kinds, but is uncommon considering the vast number of cases of such infections that occur. When nephritis does develop, it is due to the organism causing the original disease.

We are now left with a very limited literature in which some attempt has been made to elucidate the pathology of the ordinary case of nephritis. Two observers, Brewer and Councilman, record negative or partly negative results. Brewer's negative results in scarlet fever are unconvincing in view of the later discovery of the streptococcal origin of the primary disease. If they are accepted, one might almost say that the negative findings are illustrative of the difficulty in detecting the organisms or the toxins causing acute nephritis, rather than of the unlikelihood of an organism being involved. In any case, in view of Eason's results, the period of incubation of the cultures (3 days) was inadequate.

Councilman got post-mortem positive findings in the kidneys of septicaemic cases only. What else could be expected unless the kidneys are the site of a metastatic multiplication of organisms?,(and we have already rejected this supposition).

The results of Eason and of the Dicks show another aspect of the problem. They indicate that with careful technique one may, in a fair percentage of unselected cases of acute nephritis, obtain positive blood or urine results. The organisms found by both

observers in about one half of their cases were not such as can be explained by contamination etc. In most cases they belonged to the streptococcus group. but other organisms were apparently responsible in a minority of the Dicks' cases.

Positive findings by these observers, in view of the small number of previous investigators, and the less appropriate methods of these previous investigators, may be legitimately emphasised. Since their papers appeared, little has been contributed to the problem, but that little (Clausen and Allison), as we have seen, supports their views.

The post-mortem discovery of acute nephritis in fatal septic cases by Shaw Dunn and Thompson similarly emphasises the probability of nephritis being directly due to organismal infection and their analysis of the bacteriology again points to the streptococcus as easily the most frequent causal organism.

There can, nevertheless, be no question of absolute proof from such evidence. It falls far short of the requirements, say, of Koch, for proved causation.

We are, however, putting forward a hypothesis as to etiology which will, if true, make it unlikely that Koch's postulates could be fulfilled. We do not argue that streptococci are the only causes of acute nephritis, but that they are probably the commonest cause.

We do not suppose that a multiplication of the streptococcus occurs within the organ, but regard it, or occasionally some other organism as being invariably present in the body, either in the blood-stream or in some distant focus, from which its toxins and probably some of the organisms themselves escape into the bloodstream.

It does not seem certain if toxins alone, on reaching the kidney, can cause acute nephritis. Probably they can, but probably too, they rarely do. The high percentage of cases in which some authorities have found bacteriuria is strongly suggestive that usually the condition is not of purely toxaemic origin. Such negative urinary findings as are recorded by even the most careful of investigators by no means exclude this view, for we have already indicated that the organisms must seemingly make their contribution to the renal injury in the process of lysis (by production of endotoxin). As for negative blood cultures, they are

not surprising, for we are dealing with an invasion of the blood by organisms of relatively low virulence and feeble multiplying powers. Moreover, they are probably present only for a very short period at the onset of the illness. (This of course is excluding such cases as those of Shaw Dunn and Thompson, where the nephritis is the hidden feature, the infection the prominent one.)

We believe, in a word, that though these recorded results do not prove the views we are expressing, such views explain the results more satisfactorily than any others do.

We may point out that we are not creating anything like a unique picture of causation here; for, to take only one example, is not the undoubted relations of the pneumococcus to ordinary lobar pneumonia just a similar indication that a widely prevalent organism does, but only under certain rather complex favourable conditions, cause a definite type of disease in a particular organ? Similarly, also, although the pneumococcus is much the commonest cause of lobar pneumonia, it is not the only possible cause.

SUMMARY OF SECTION I.

1. The etiology of nephritis, acute and chronic, has been considered in the light of

(a) Figures compiled from the U.S. Surgeon-General's statistics, 1917-1919.

(b) An analysis of cases of acute and chronic nephritis in children (patients in the medical wards of the Royal Hospital for Sick Children, Aberdeen.

(c) A review and analysis of the literature.

(d) A short analysis of a number of consecutive post-mortems at Aberdeen Royal Infirmary.

2. The evidence from all these sources is almost unanimously in favour of the view that the cause of both acute and chronic nephritis is bacterial and toxic.

3. The Surgeon-General's statistics reveal the fact that the relationship of infective conditions in general to acute nephritis is very limited, and that it is definite only in conditions where the case mortality is so high as to be consistent with the view that only a low degree of selectivity for the kidneys is possessed by the organisms concerned.

4. Included in the diseases with an incidence of nephritis too low to be regarded as more significant

than other infections are a number of conditions (measles, smallpox, tonsillitis, diseases of ear and nose, etc. etc.) commonly supposed to have a special relationship. (This is not apparently true of children).

5. The only exception, and that a very distinct one, is the incidence of acute nephritis in scarlet fever, a streptococcal infection.

6. Confirmatory evidence, suggesting a special role for the streptococcus in many cases of acute nephritis was found in clinical and post-mortem material examined, and in the literature dealing with similar investigations.

7. In acute nephritis in children discoverable focal origin or definitely related acute infection is found to be usual. It is so frequent as to suggest that in the minority of cases in which a cause is not discovered, there is really a similar method of production. In adults, evidence of the causal significance of focal sepsis present is more difficult to obtain, but reasons are given against regarding this as indicative of a different etiology.

8. A high percentage of speedy cures of acute nephritis in children following on removal of septic foci is claimed as a strong argument in favour of the causal significance of the septic foci, as are other similar

special indications of relationship.

9. It is held that the action of these septic foci probably depends in part on toxin production, and in part on actual bacterial invasion of the bloodstream, but this invasion, if nephritis in the ordinary sense is to result, does not lead to a local multiplication of the organisms in the kidney. If such a multiplication occurs, the disease produced is likely to be either suppurative nephritis or on the border line thereof ("acute infectious nephritis" of Campbell and Rhea.)

10. The mode of action of circulating bacteria and their toxins which leads to the production of acute nephritis is suggested to be a damage produced by the action of exotoxin combined with an endotoxin set free by a lysis of the organisms trapped in the glomeruli. It is suggested that the frequency with which bacteria are found in the urine in acute nephritis in the more careful researches in the literature, is so great as to negative the suggestion that, usually, at any rate, the toxins (exotoxins), are acting alone. At the same time, there is a certain distinct percentage of negative findings in the urine. Whilst these are consistent with an origin by toxaemia alone, they do not particularly favour this assumption, for they are also consistent with the other view; negative results might be due to more complete lysis of the bacteria in the glomeruli,

or, more likely, to the existence of only a very brief initial septicaemia, the toxaemia alone acting later. Very few cases of nephritis are available for detailed examination from the time of onset. (Further discussion of some of these points will be given in section 2).

11. It is suggested that the peculiar role of the streptococcus may be explained by some difference in the nature, or, more particularly, probably in the amounts of endotoxin and exotoxin producable by it as compared with other organisms. A streptococcal infection probably increases in virulence usually by increase in the amount of toxin produced, rather than by enhanced power of multiplying metastatically in different tissues. Or, in other words, the streptococcus is not a typical pyaemia-producing organism. Nevertheless, the potency of its toxins causes it to be in many instances a very serious type of infection. Many other organisms acquire greater virulence in a different manner (or a different sense) by becoming capable of multiplying in distant foci and causing pyaemia. Short of producing this, they tend, from lack of toxin-producing power, to cause relatively slight infections. (We refer to such organisms as the staphylococci, b. pyocyaneus, coli-typhoid group etc. A few, such as tetanus and diphtheria, are not included in this category, but the reasons for their

relative unimportance in human nephritis will be discussed in Section 2. Meanwhile, it might be noted that in any case they do not satisfy the other requirements of the theory - bacteriaemia.)

Now, if such a difference be admitted between streptococci and the other organisms with which we are contrasting them, it immediately becomes apparent why, according to our theory, streptococci are best adapted for the production of acute nephritis; for they are potent toxin producers, they are capable of blood invasion, and nevertheless they are unlikely to multiply locally in the kidneys and produce pyaemic abscesses. Before becoming possessed of the virulence necessary for such multiplying power, they are likely, by combination of endotoxic and exotoxic action, to be able to cause acute nephritis. Other organisms, circulating similarly, and being lysed similarly in the glomerular tufts, will generally fail, by reason of feebleness of endo- and exo- toxic action to produce more than minor renal changes, and, if the infection becomes heavier, or increases in virulence. the tendency will be to convert the picture from a mildly"toxic" kidney to a pyaemic kidney rather than to acute nephritis. This is illustrated in particular by the post-mortem statistics analysed.

12. A similar cause and mechanism is supposed to be at work in the production of chronic nephritis (i.e.

intermittent bacterial bombardment of the kidneys from septic foci, together with toxaemia from these foci; the foci being chronic, and the infections of low grade; similar bacterial lysis occurring in the glomeruli).

13. There is in the evidence bearing on the bacteriology of chronic nephritis, as in that bearing on the bacteriology of acute nephritis, a tendency to implicate the streptococcus as the commonest organism at work, but its predominance is less marked in chronic than in acute nephritis.

SECTION 2.

The previous section has considered most of the evidence obtainable on the etiological problem. For further light we turn to experimental evidence. This evidence may also, we hope, contribute to that other problem of the course or sequence of nephritic changes in the kidney which has scarcely received any elucidation at all from the types of evidence we have hitherto considered.

The inadequacy of our knowledge of the sequence of changes in nephritis is obvious. Only a rough and ready classification of the various appearances in the nephritic kidney is possible, and the groups mingle and fade into one another in a perplexing manner. The sequence of changes is in doubt almost from the start. Indeed, the problem is such a puzzling one that it is customary for the clinician either to content himself with an entirely clinical classification of his cases, or to associate the clinical syndromes with types of pathological appearance which would, not infrequently, be completely falsified on post-mortem examination. More particularly is this the case if, as often, each syndrome is referred merely to a particular size and colour of kidney. Clinically similar cases may fall into quite different groups (at least on the usual systems of grouping); and kidneys within the same pathological group may have come from cases of widely different clinical history.

The first problem, and a very intersting one, is presented at the very onset of an attack of acute nephritis. The kidney unit consists of the glomerulus with its capsule, and the tubule. Which of these is initially infected? Or may either, or even the interstitium, show the first effects?

There is no acute nephritis of any severity which does not come to affect in some degree glomerulus, tubule and interstitial tissue, and it may be that all are affected more or less simultaneously, but there is no justification for starting by assuming this.

Indeed it seems more likely that the particular set of conditions present will render one or other of the structures more specially susceptible to the poison causing the condition.

After death, cases of acute nephritis frequently show a much heavier incidence on one structure than on another, but this, while suggestive, does not prove that the affection of that part was initial. The question is complicated, for one thing, by the arrangement of the blood supply of the kidney. It is now certain that the blood supply of the tubules is practically entirely dependent upon a capillary plexus around them derived from the efferent arterioles of the glomerular tufts. This means that any severe lesion of the glomerulus is bound, by interference with the blood supply, to cause secondary changes in the tubules. (To a lesser extent a secondary - atrophic - change is possible in the glomerulus of a severely damaged tubule, though scarcely in the acute stage).

Further, the excretory function of the organ is itself bound to alter the concentration of poisons at different parts, this whether the poison is itself excreted or not, and whatever theory of renal function we adopt. Unfortunately, views of renal function are not yet quite settled, and there is therefore an inevitable difficulty in making deductions from them.

Another difficulty lies in the manner in which, in the glomeruli, histological evidence of acute damage tends to lag behind quite distinct evidence of functional disturbance. Kinloch (76), amongst others, points this out, instancing a case of scarletinal nephritis dying within 3 days of the onset of nephritis, in which the kidneys, on cursory microscopic examination, might have been pronounced normal. Careful examination, however, revealed an acute and practically pure glomerular change (swelling of capillary walls, endothelials, etc.) as the cause of symptoms and death. Bearing in mind this relative difficulty in detecting damage to the glomeruli, one feels that it is possible that in more cases than is obvious the initial and main lesion is in the glomerulus and its capsule. Certainly it is remarkable how many of the most fulminant cases of acute nephritis show little beyond glomerular change. These are naturally the cases where examination of the kidneys is possible at the earliest stage of the disease.

Another point of some interest is to find whether functional and structural changes in the capsular epithelium of the glomerulus accompany chiefly changes in the glomerular tuft to which they are geographically related or in the tubules to which they are related developmentally.

It may have been rather too readily taken for granted that the types of incidence were glomerular or tubular, using the former term to include the capsular epithelium, and it is possible on theoretical grounds that sometimes capsular plus tubular changes and endoglomerular changes might form an equally effective contrast. Embryologically, the whole tubule, including the invaginated capsular portion, is of similar (mesodermal) origin. Down from the capsule to a little below the last portion of convoluted tubule, the tubules originate from one portion of mesoderm. The collecting tubules etc., which soon join up with the other part, arise also from mesoderm, although in a different site. On these grounds, changes in the capsular epithelium might be expected to develop along with changes in the tubules, particularly in the convoluted tubules.

Such considerations sufficiently justify some investigation first of all of the mode or modes of onset of acute nephritis, and of the possible influence in this matter of different causal agents.

It is by no means certain that such an investigation will unify the whole series of cases, but it is at least worth while to see whether or not some of the varieties of appearance may indicate in reality more of difference in stage, and less of fundamental difference in type, than is suggested by a perusal of the various labels attached to individual cases.

Difficulties, however, by no means cease with the manner of onset of acute nephritis. We do not know exactly the further course of an acute nephritis in cases where complete recovery does not take place, nor are we sure if clinical "complete" recovery is also pathologically complete. As to the stages by which acute nephritis advances to the various forms of granular contracted kidney, we know comparatively little.

Many cases, too, of granular contracted kidney have had no acute attack, and the mode of production of these also requires to be considered.

The vagueness of our knowledge on all these points is striking in view of the great importance and comparative frequency of the disease, and in view of the abundant post-mortem material. It is in this last statement, however, that the root of the difficulty lies. Abundant as is the post-mortem material, it gives in each case as it were but a photograph of the appearances at some one instant, and it is exceedingly difficult in any given case to gather from that photograph what eventually would have been the appearance had the patient lived or what were the appearances at an earlier stage.

Such a state of affairs seems to point strongly to one line of investigation in particular, namely to animal experiment. Were it possible to produce a chronic nephritis in suitable animals, the difficulty of studying appearances at intermediate stages would disappear.

Let us, however, before going any further, summarise briefly the salient points of our knowledge of nephritis in man with a view to noting where difficulties of interpretation may exist.

Alterations in the Kidney in Nephritis in Man.

A great part of this summary is a slightly modified synopsis of the descriptions given by Shennan (155).

It is generally accepted that in acute nephritis the inflammatory process affects all the constituent elements of the kidney - glomeruli, tubules and interstitial tissue, but does not necessarily affect all of these equally, or, we might add, simultaneously. Acute nephritis is frequently classified, therefore, as glomerular, tubular (desquamative, catarrhal), or interstitial, according to the particular change which predominates.

In all these types both kidneys are as a rule diffusely affected, though microscopically a varying proportion of the units is frequently seen to be distinctly less affected than the remainder.

The organ is swollen and the capsule strips readily. The outer surface is usually greyish-pink. The cut surface shows a rather widened cortex which may be either pale, or pink from congestion, and, if the glomeruli are specially affected, these stand out as small reddish-brown points. Some haemorrhages may be present in the boundary zone. The medulla, particularly in the boundary zone, is congested, and the pelvis also shows some congestion. At a later stage, the swelling of the cortex becomes more marked, its opacity increases, and it becomes greyish white, possibly with yellowish spots of fatty change.

Microscopically, the glomeruli are congested. They may show no further change, or there may be escape of R.B.C. and albuminous material between the capillaries

of the tuft and into the glomerular spaces. The endothelium of the tufts is swollen. The capillaries and afferent artarioles of the tufts may show hyaline swelling with resultant narrowing or occlusion of the lumen. There is leucocytic infiltration around the afferent arterioles, into the glomerulus, and the glomerular space.

The "secreting" portions of the tubules show cloudy swelling and catarrh, frequently with fatty change; in addition, some of the epithelial cells are breaking down, and the lumen may contain fibrin, casts or R.B.C.s.

The interstitial tissue shows oedema and congestion, and sometimes a considerable accumulation of cells, chiefly mononuclears with a few polymorphs.

As already mentioned, however, the changes in one of the three elements, glomeruli, tubules or interstitium, are likely to be more prominent than those in the others in an individual case.

It would be agreed by most that the more fulminant cases tend to show as a rule chiefly glomerular changes, less often predominant interstitial changes, and still less often mainly tubular changes.

At this point, we might perhaps interpolate our first question. In what degree are the various relative incidences of acute nephritis post-mortem (on interstitial tissue, glomeruli and tubules) compatible with an initially similar method of onset? Or the question might be put in alternative form - are some at least of the varying incidences not indications of varying stage, rather than of true variation in site of primary incidence? If no degree of simplification is possible on these lines, can ascertainable differences of cause be held to account for the differences in type?

Acute nephritis may, it is generally recognised, either show recovery, or go on to some one of the forms usually designated as "subacute nephritis". Whether or not the "recovery" kidneys show some permanent damage is not definitely settled.

In subacute nephritis, the kidney is still enlarged, often much enlarged, and the cortex is, as a rule, pale, widened and greyish, generally showing opaque yellow spots of fatty degeneration, and often showing also coarse haemorrhagic points. To such an organ, the name of "large" white kidney" is frequently applied, or, if the haemorrhages referred to are present, the term may be modified to "large pale coarsely mottled kidney".

Both of these types are sometimes included in the name "subacute parenchymatous nephritis".

In some cases, large kidneys are found, where, though at first the surface may not be granular, or the capsule adherent, such, and other evidences, of interstitial change may develop while the kidney is still large. The cortex, too, may be mottled by darker purplish markings indicating vascular connective tissue. Retention cysts may be noted. This is the variety known as the "large pale finely mottled kidney" (subacute diffuse nephritis).

Microscopically, in all these cases of subacute nephritis, a rather similar type of change is found, but the predominance of the changes in the different structures varies.

In all, the convoluted tubules tend to show fat in many cells. The apices of the cells are broken off, leaving a flattened lining to the tubules. Epithelial, hyaline, granular, fatty and (in haemorrhagic forms), blood casts, may be seen in the lumen. There may be regenerative proliferation of epithelial cells.

These tubular changes are more marked in the other two subdivisions than in the interstitial one, but are present in it too.

The glomeruli may show proliferation and desquamation of the epithelium of Bowman's capsule, and blood in the glomerular space. The changes in the glomeruli are more marked in the interstitial form, in which especially we find the familiar " epithelial "crescents", between the layers of which connective tissue may at a later stage be laid down. The glomerular capillaries may become separated up by connective tissue, and may in time become obliterated and hyaline by contraction etc. of this connective tissue. Meanwhile, many other glomeruli may remain normal.

The interstitial tissue may show a slight cellular increase in all forms, but the change here is most marked in the interstitial type, where it may either be fairly diffuse or more marked along the interlobular and other vessels. The degree of glomerular and of interstitial change present generally show some correspondence.

At this point a host of questions might be put, but we are interested particularly in one aspect. Since glomerular and interstitial changes usually go to a great extent together, is this because the one (probably the glomerular), leads to the other?

Also, going further back, what type of acute nephritis is it which leads to the " glomerulo-

interstitial subacute type? Must it always be glomerular, or may it be interstitial or tubular?

It is here that the biggest hiatus exists, for it is probably easier to bridge the gap between subacute interstitial nephritis and chronic interstitial nephritis (markedly though the kidneys may differ), than to trace the first steps in the development of a progressive nephritis from an original acute attack.

Next come the appearances describable as chronic nephritis. The kidneys here are for the most part contracted and granular, and for the different varieties of this kidney a number of descriptive terms have been coined.

The"small red kidney", with its granular surface, thickened, adherent capsule,and narrowed cortex, is often histologically a " chronic interstitial nephritis"- i.e. it shows widespread, though not uniform, increase of connective tissue. The histological picture is often much as in subacute interstitial nephritis, butthe connective tissue is denser, and perhaps rather more diffuse. The vessels are often greatly thickened.

As with all naked-eye classifications,it is, however, impossible to tell always what precisely will be the histological changes.

There is much doubt as to the earlier history of this kidney. It seems unlikely that it develops phase by phase from the unusual"acute interstitial nephritis". The name applied is therefore rather misleading. The histological appearances imply a close relationship of the interstitial to the glomerular change. Histologically, it is difficult to tell in an individual case, whether or not an acute phase was ever gone through. When, however, an acute or subacute phase has pre-ezisted, it seems probable that the kidney concerned has passed through the form just described as subacute diffuse nephritis.

In the absence of any indication of an acute or a subacute phase, the problem arises of whether or not we can correlate its development in any way with the "repeated minor insults"(bacterial), which have been suggested as causal in its production.

A further complication is introduced by the existence of another type of"small red kidney" in which a more markedly irregular type of contraction has occurred, chiefly in the areas supplied by arteries obviously very sclerotic. The capsule need

not in the typical case be diffusely adherent or thickened, but thickening and adhesion are present over the irregular depressions. Such a condition justifies the name of arterio-sclerotic kidney, and suggests an initial, or at least an early, affection of the vessels as being concerned in its production. It is ,however, open to grave doubt whether this type of kidney does not represent, equally with the other contracted kidneys, simply a nephritis, an inflammation of the kidney. It is very questionable indeed if it is merely an atrophy, resulting from the renal part of a generalised arterial sclerosis. The arterial sclerosis is often limited to the vessels within the kidney, and slight, absent or of different type in the vessels elsewhere, including the main renal artery. (Klotz 79). Moreover, the most advanced cases of generalised arterial sclerosis may not be accompanied by typical "arterio-sclerotic kidney".

A further difficulty in clarity of classification, and one which tends to strengthen the bond of association between intrarenal arterio-sclerosis and renal inflammation, is that all degrees of combination of arteric-sclerotic kidney and chronic interstitial nephritis are met with.

Next, we have the other kind of contracted kidney, the "small white kidney". The microscopic appearances may be as before, but at other times the increase of connective tissue, though present and fairly diffuse, is not so great, and the reduction in size seems to depend more on an absolute decrease in the parenchyma. Such increase of connective tissue as is seen may be partly just an apparent increase, due to its condensation by loss of parenchyma. The factors which tend to the production of this type of appearance as against the other, are not clear. It might be held to result from subacute parenchymatous as against subacute interstitial nephritis, were it not that it apparently may exist in some cases without a history of previous attack. (Rose Bradford kidney).

A widely adopted classification of chronic nephritis, may be mentioned here. It is that of Senator (122)

1. Chronic parenchymatous nephritis (chronic diffuse nephritis without induration.)

2. Chronic interstitial nephritis (chronic diffuse nephritis with induration.)

   (a) Primary chronic interstitial nephritis.
   (b) Secondary chronic interstitial nephritis.
   (c) Arterio-sclerotic kidney.

3. Mixed type - a combination of 1 and 2 - i.e. diffuse nephritis.

The above summary is obviously not one of a sequence which is entirely satisfactorily solved. The chief reason for our inadequate knowledge is, as has already been mentioned, the impossibility of studying the progress of the renal lesions stage by stage in man; and it is this argument that points to the desirability of a study of experimental nephritis, in which, although such a study has its own serious drawbacks, this particular difficulty may possibly be overcome.

Early in the history of the study of nephritis, the avenue of animal experiment began to be explored, and over a long period a great mass of literature on this aspect has been produced. The results have not, however, been as conclusive as might have been hoped for.

Organisms and their toxins which seemed to have been definitely inculpated in cases of human nephritis, to judge from researches such as have been discussed in the previous section, have failed repeatedly in a variety of animals to reproduce the disease satisfactorily. Renal changes, inflammatory in nature, and in that sense therefore a nephritis, had frequently resulted, but a complete reproduction of the picture of progressive nephritis as it occurs in man has not been secured.

The numerous simple chemical poisons which have been used in producing nephritis in animals, are obviously for the most part not concerned in the causation of human nephritis, - although the long continued action of lead or borax may just possibly have a bearing on some cases of chronic nephritis, but they serve to illustrate one essential point - viz. that the kidney, as an excretory organ, may be injured by any one of the innumerable noxious substances which it may be called upon to excrete.

Although we note these difficulties in the experimental line of investigation, there is abundant justification for its consideration and its further pursuit, for, as we have pointed out, difficulties just as serious follow the investigator who confines himself to the study of human cases.

We propose, therefore, to deal next with the evidence of experimental nephritis, and to present it in the following order,- first, a study of the literature, and, secondly, personal experimental results.

Literature on Experimental Nephritis.

This literature is very voluminous, contributed to by workers of many nationalities and over a long period of years. A small number of contributions have appeared in journals to which we have been unable to gain access, and a number of others presumably exist of which we have found no record. We believe, however, that the more important papers are considered here; and. indeed, a number have been included which, from their vagueness on points essential to us, are of comparatively little assistance.

While it has for long been generally agreed that a toxic or infective origin is responsible for nephritis in man, experimental work has often dealt with lesions produced by substances altogether outwith this category, and exceedingly unlikely as causes of nephritis in man. The adoption of such lines of investigation has a simple enough explanation in the difficulty in producing marked changes, and especially in producing progressive changes, in animals, with bacteria or their toxins.

On the other hand, it can scarcely be doubted that the various chemical substances so often employed cannot have affects completely analogous to those in human nephritis, so that the usefulness of this alternative line of investigation has its distinct limitations.

Taking the two lines of experimental investigation together, however, a considerable total of useful information has been obtained. The chemical experiments have furnished us with the better basis of the two for a chemical study of renal function in marked impairment of the organ, for they, or at least a number of them, readily bring this about. On the other hand, bacteria and their toxins, while on the whole producing less marked changes, are more suitable

for the study of the site and mode of renal damage as it probably occurs in man.

We would urge the importance of studying an additional and rather obvious point which seems of some importance, but to which curiously little attention has been directed in the literature. The simple chemicals referred to are crystalloids, the bacterial toxins are very probably colloids. Certainly they are relatively complex molecules. On the one hand we are dealing with relatively simple molecules, which are excreted in part in the urine. This excretion, whether we adopt the older or the modern view of renal function, does not arise merely or primarily from the damage the poison produces in the organ, but from the fact that its simple chemical constitution places it amongst the group of substances which the renal apparatus attempts to excrete. The damage is produced in excretion. The excretion is not simply the result of damage.

The bacterial toxins and allied substances are, on the other hand, complex molecules, and are probably not excreted until they have damaged the renal structures. Their excretion when and if it does occur is subsequent to the damage to the kidney. For the moment we are deliberately avoiding reference to either of the rival theories of renal function, and endeavouring to establish our point if possible on a broad basis which will not depend on the acceptance of either theory.

The exact chemical nature of toxins is in doubt, but our view is based on a generalisation as to their nature, which, so far as one can judge from the literature, has not been seriously challenged. They are complex molecules, whether protein or lipoidal. Very probably they are colloids. It is on this difference that we base our expectations of obtaining a rather different type of renal lesion with them than with simpler chemicals; and it is by following up this reasoning that we shall later attempt to explain certain fundamental differences between experimental chemical nephritis (and occasional chemical cases in man) and ordinary human nephritis.

Nature of Toxins etc.

Older views were strongly in favour of a protein nature for toxins, but, even in 1906, Oppenheimer and Mitchell (21) stated that the matter was not proved, but that toxins were certainly of high molecular weight. As already said, this is the point on which we have based our distinction, and it is the point

on which least controversy has arisen. The distinction between simple chemicals and toxins is emphasised from another angle by the continued failure of observers to produce antibodies to true crystalloids (excepting the crystalloid albuminoids) (Oppenheimer and Mitchell 121 and Morgenroth 105).

Recently various lipoids have apparently been successfully used as antigens (Warden 165 Warden, Connell and Holly 166 Fairley 49 Much 106 and a number of others), but these also are complex molecules.

If we pursue the matter a little further, on the lines now of the modern view of renal function as expounded by Cushny*(33) we are naturally tempted to seek for direct experiments on the filterability of toxins. Roux and Yersin, quoted by Oppenheimer and Mitchell (121) say that diphtheria toxin diffuses through parchment. Chassen and Moussu (21) state, however, that it does not diffuse through membranes made from the organs of animals and Rodet and Gulchoff (142) note that it does not diffuse through collodion. Such experiments would incline us to believe that the unimpaired glomerular filter would retain toxins.

Direct experiments with the urine are not so entirely satisfactory as might at first seem. We are dealing with agents calculated to damage the kidneys, and often producing definite albuminuria, itself an indication of abnormal glomerular permeability. There can be no possibility of denying that subsequently to causing damage, toxin may pass through the filter. Indeed, everything would point to this occurring, and such a phenomenon may, we will see, be invoked to explain one of the phases of renal damage in acute nephritis. The evidence of those who have actually sought for toxins in the urine is conflicting, and perhaps the conflict may best be resolved by just such an

*We believe this to be much the best attempt at a coordinated explanation of renal function. In discussing individual points in this section, opportunity will be taken to compare the merits of the old and the modern views, both in general and in relation to the particular problems which crop up.

explanation as we are putting forward. Those observers examining the urine in early stages may not find it, while those examining later may. Thus Goldberg (55) working with tetanus toxin, observed a remarkably rapid disappearance of the toxin from the blood after infection (most being gone in less than an hour). Seeking for an explanation of this he examined the urine, but found no trace of toxin. Obviously, this was an early examination. Cobbett (26), on the other hand, claimed to find diphtheria toxin in the urine of patients with diphtheria. Although he gives no details, it is likely, dealing with human patients as he did, that his observations took place much later in the disease, and after the glomerular filter had become abnormally permeable.

This reasoning establishes a strong case for the investigation of the results in the chemical and bacterio-toxic groups in order to ascertain whether or not any differences in site or mode of action can be made out between them. Much comparison and contrast has been recorded between the action of individual agents of the two different groups, and almost as often between the action of two agents of the same group. The summed result of the great series of such narrowly based contrasts is exceedingly confusing. The differences between two chemicals as emphasised by one author have frequently exceeded those described between a chemical and a bacterial agent by another, and we are really without a properly correlated review of the changes produced by the one series of agents as against those produced by the other. It is with a view to finding if such ascertainable differences actually exist that this review and to a certain extent our own subsequently recorded experiments have been constructed. We cannot be sure that we shall find such differences, but the type of the two agents, simple chemical on the one hand, and bacterial or toxic on the other, is so widely different that the question is worthy of investigation.

Spontaneous Nephritis etc.

Both in our own experiments and in preparing this review, we have encountered certain difficulties and fallacies incidental to the animals used, which have such an important bearing on the interpretation of experimental findings as to necessitate preliminary consideration. This is the more important, as we will find it obvious as we proceed with the review, that various writers have in different degrees appreciated these difficulties and fallacies. Consequently, in many cases where consideration or appreciation has been scanty or absent, we shall have occasion to modify or discard the author's interpretation of his own findings, and shall lay stress upon what is apparently the more scientific work reported.

Is spontaneous nephritis common in animals? The practically unanimous answer to this is "yes", but the type of nephritis found is in an overwhelming proportion of cases quite distinctive. It is a focal nephritis, with interstitial and tubular changes. Its chronic form is the confusing one, for this leads to some scarring of the organ and dimpling of its surface. The essential difference from chronic nephritis in man lies in the presence of interstitial overgrowth combined with an absence of severe glomerular damage. It is further distinguishable from ordinary chronic interstitial nephritis by its focal distribution, with wide areas of intervening kidney tissue which are normal. We will not concern ourselves greatly about the spontaneous acute renal lesions of animals. In an "acute" experiment, the chances of the coincidence of acute "spontaneous" change with the injection of renal poisons is exceedingly small, and only a small number of experiments and controls is needful to eliminate the fallacy; nor ought there to be any difficulty with obviously subacute or chronic "spontaneous" lesions in animals subjected to acute intoxication. Yet, strangely enough, the literature is not without examples in which lesions, obviously of some standing, and, incidentally, spontaneous, to judge from the histological appearances, have been described as effects of an injection given a very few days previously.

Our real source of serious fallacy, then, will lie in subacute or chronic "spontaneous" lesions, where these happen to coexist in an animal subjected to repeated inoculation in an endeavour to produce chronic nephritis.

Many excellent descriptions of such lesions, particularly in rabbits, the animal most commonly used, have been given. Spontaneous glomerulo-nephritis in rabbits, if its exists, must be exceedingly rare, but focal tubular and interstitial changes are very common, and have been admirably described by, amongst others, Le Count and Jackson (87) Bloomfield (11) and Bell and Hartzell (9).

In the early stages there is microscopically a varying amount of round celled infiltration around the smaller veins, especially of the boundary zone, but sometimes spreading along the vessels into the cortex. Within these infiltrated areas, the tubular epithelium is necrosed, and the proximal portions of such tubules often show dilatation or atrophy. Gradually the infiltration extends till it comes to occupy a wedge-shaped area with its base on the cortical surface, and its apex reaching perhaps into the medulla. Ultimately, fibrosis commences in such areas, and the degenerative and atrophic changes in the tubules of the involved area are accentuated so that sometimes the remains of some of the tubules are made out with difficulty. In the earlier stages, a plum-coloured spot on the cortical surface may indicate an area of infiltration, in the later stages a pinhead depression may occur at that site. The glomeruli, though shrunken in these areas, show no marked alteration, and no alteration at all suggestive of glomerulo-nephritis. A few glomeruli may be fibrotic. (Microphotographs 11 & 12.).

Although in this way a granular kidney may be produced, the capsule is never very adherent over the pits, and, most important of all, even in the worst cases, the change remains clearly focal, and the greater part of the kidney substance seems to be unaffected. There is no reason to believe that the animal with such an organ is not possessed of functionally efficient kidneys.

Various percentages of rabbits (from 10 to 90%) have been said to be affected by the condition to a greater or lesser degree, and it has long been evident that the percentage incidence varies more with the particular batch of animals dealt with than with any matter of age, sex or breed. (Bloomfield 11).

Only recently have suggestions been made with regard to its etiology.

McGovern (97) in 1920 suggested that it was related to toxaemia following coccidiosis.

Leiter (88), writing in 1924, states that the etiology is unknown, but, from the histological appearances, probably of embolic nature. Even before this, however, work had been published which so closely accords with what one might expect, that it may provisionally accepted as correct. The fact that the condition varies in incidence more with the batch of animals investigated than with any other circumstance strongly suggests a cage infection, and the distribution of the lesions suggests an embolic origin. Both these observations fit in with the explanation given by Wright and Craighead (173) who found the well known spontaneous encephalitis of rabbits to coexist in many cases with spontaneous nephritis, and in the focal lesions in both organs found a microsporidium belonging to the sporozoa. Similar organisms have been described in spontaneous encephalitis by Doerr and Zdansky (41) and by Levaditi, Nicolau and Schoen (89).

Even before this, Twort and Archer (161) had described in rabbits an encephalitis and nephritis of evidently common etiology, though they did not discover the causal organism, which they regarded as a filter-passer. They describe a severer form of the nephritis than other observers have recorded, one which is actually fatal, with a high blood urea and albuminuria. This apparently represents a very unusually diffuse form of the lesion, and an unusual end result. The microscopic changes they record are similar to those of other observers, except for the more diffuse nature of the lesions in their fatal cases.

The fact that the disease probably shows at least two elective sites in the animal leads to a further consideration. Infected animals may have a latent encephalitis only, but the injection into such animals of any poison which can damage the kidney even to a small extent may quite conceivably lead to the establishment of the infection in that organ also. This is precisely the suggestion required to clear up much that is otherwise anomalous in the records of experimental nephritis. Lesions similar to those occurring spontaneously have frequently described in inoculative and especially in repeatedly inoculatived animals. In spite of their suspicious appearance, they have commanded a certain attention because the majority of observers have found such lesions more frequently in injected than in control animals, and more marked after longer than after shorter courses of injections. The explanation is not far-fetched, for, as investigators of encephalitis found to their cost, latent encephalitis is exceedingly common in many batches of rabbits.

In the literature, two significant facts are obv ious and speak for themselves.

1. The literature is full of chronic changes "produced" by various injections. These are of uniform type. The type is that of spontaneous nephritis, not of chronic nephritis as found in man.

2. Changes of this nature have been described after injections of substances of every possible nature, after every possible period of time, and after single or numerous injections.

It does not appear, although the question has not been so thoroughly investigated, that the fallacy of a spontaneous non-glomerular nephritis, can be excluded in any others of the usual experimental animals. It appears to be the case that at least the majority of species of lower animals so far used are to some extent prone to a similar type of spontaneous nephritis.

It appears also, and this is probably the key to our difficulty in producing progressive nephritic changes in animals, that progressive glomerulo-nephritis is exceedingly rare in them. Roth and Bloss (145) in 7,000 necropsies on sheep, found only 23 cases of chronic nephritis, of which not one was a true diffuse glomerulo-nephritis.

With these preliminaries we will now proceed to a consideration of the result obtained by various investigators with the two groups of substances used, the chemical, and the bacterial or toxic.

Nephritic Changes Induced by Chemical Substances not of bacterial origin.

A large number of chemical substances have been used from time to time for the production of nephritis. Some have been but rarely used, others have been used repeatedly. The main underlying principle seems to have been the same in all. All are general protoplasmic poisons and probably different from other simple chemical poisons chiefly in that they are more largely excreted by the kidneys,

than by the skin, the bowels, the lungs, etc. It is probable that with some of them there is in addition some selective action on the renal cells, in the sense of an actually higher sensitiveness of these particular cells to the poison than is possessed by other cells, but it is not likely that this is a feature common to all the poisons used, nor is it in any way necessary before harmful results can selectively be produced in the kidneys. If the kidney is engaged in excreting a substance, whether we adopt the old or the new views of renal function, it must necessarily be present in higher concentration in the renal cells than in those of other organs, and must therefore, apart from any special sensitiveness of the kidney cells, be more likely to produce lesions there than elsewhere. On the modern view of renal function (Cushny 33), to which we will endeavour to relate results with individual substances, the relatively simple molecules of these chemical poisons would pass through the glomeruli with the dilute filtrate and become progressively concentrated in the tubules as the filtrate passed down. This would lead us to expect lesions in the lower "secreting" cells especially, unless the particular poison had some degree of selective action on a special portion of the tubule. The less highly differentiated and less sensitive collecting tubules would, though exposed to a high concentration, naturally tend to escape by reason of their lesser sensitiveness. This is in accord with the general law that a protoplasmic poison is effective in highest dilution on the most specialised cells.

It is, then, the simplicity of the requirement, namely, that excretions should be partly through the kidneys, that explains why such a diversity of unrelated chemical poisons have been more or less successfully used for the production of renal lesions. At the same time, this underlying unity encourages us to search for some fundamental resemblance in type between the various forms of chemical nephritis. Corrosive sublimate and sulphuric acid, say, may kill cells by widely different methods, and the appearance of the degenerating cells may differ, but as these appearances are in neither case likely to be such as characterise ordinary human nephritis, they are of relatively little importance from our point of view. What does interest us is to discover whether the site of the lesions. their functional results, and any permanent results in the kidney, are similar when different chemicals are employed.

Turning to individual substances, we shall give a brief record of the investigations on the chief substances as presented in the literature, with special reference to the type and site of lesion resulting.

Sulphuric Acid.

Munk and Leyden (107.) claim as the chief lesion an increase of nuclei in the interstitial tissue of the kidney, with cloudy and fatty changes in the tubules.

Litten (91) found similar changes, but not until the second week after injection.

Burmeister (17) found simply degenerative changes in the epithelium of the tubules.

Summarised, it would appear that tubular lesions have been found by all investigators noted. whilst two of the three have observed an inflammatory increase of nuclei in the related interstitial tissue. None of the investigators claim to have produced chronic changes.

Chromic Acid and its Salts.

Chromic acid and its salts have been repeatedly used to produce experimental nephritis. The earliest allusion to chrome as a substance definitely producing nephritis is possibly that by Gergens (54). Amongst other early workers might be noted Kabierski (69) and Posner (136), who described it as producing a tubular nephritis, though the former also claimed after six days some cellular infiltration around the bloodvessels and commencing proliferation of cells in the interstitial tissues. Numerous subsequent writers have given detailed descriptions of the acute lesions. On the essential fact of the preponderance of the tubular lesions, all are agreed. Minor differences exist in the descriptions, some recording a little leucocytic infiltration between the tubules, others very minor glomerular changes, but hardly any claim any real prominence for these.

The one exception to this is perhaps MacNider (99), who states that in the earlier stages there is a vascular injury produced which is rapidly followed by a tubular lesion which soon dominates the picture. He has no support from others, however, unless we include as supporting him Kossa (84). Kossa was chiefly concerned with the accompanying glycosuria, but mentioned haemorrhages as being prominent in the kidneys.

Schlayer and Hedinger (151), Heincke and Meyerstein (61), Ophüls (118), Hellin and Spiro (62), Pearce, Hill and Eisenbrey (129), Weber (168), Ruschaupt (148), Austin and Eisenbrey (4), and Kahlden (70) all describe a special, though not necessarily an exclusive affinity for the secreting epithelium. Ponder (135) may be named amongst those who claimed to have produced interstitial as well as tubular changes in acute experiments.

By repeated injections, the tubular changes can, it is agreed, be maintained indefinitely if the animal lives. These continued tubular lesions, with now regeneration as well as degeneration of the tubules, and in the regenerated tubules frequently a lower type of epithelium than the normal, are the only lesions constantly described. With this result, which coincides with that of our own experiments, recorded later, we agree. Such increase of interstitial tissue as we found were very slight, was related to slightly thickened bloodvessels, and, even if not spontaneous was in no way analogous to chronic interstitial nephritis; nor was it of the type apparently likely by further progression to develop to that condition.

Some have, however, described considerable increase of the interstitial tissue. Burmeister (17) and others to whom he refers give such descriptions.

Christion, Smith, and Walker (22) found in rabbits and guinea-pigs subjected to repeated injections of potassium bichromate marked focal interstitial changes. Their descriptions of the lesions produced tally with those of spontaneous nephritis.

As we ourselves and others have failed to produce significant interstitial change, and as the lesions produced by those claiming success are similar to those of spontaneous nephritis, we are strongly inclined to the view that chromic acid and its salts produce an acute nephritis of earliest and greatest influence on the tubules, that these can be sustained for a variable period by repeated injections until the

animal dies without progressive glomerular changes or significant increase in the interstitial tissue, though not necessarily without acute glomerular change if the dosage be at any time raised sufficiently.

By "significant" increase of interstitial tissue we denote a fibrosis of a degree and extent likely to produce a granular contraction of the kidney, or alternatively to contribute materially to any renal insufficiency present.

The portion of the tubule most severely affected will be discussed along with the description of our own experiments, where reference will also be made to results as to the excretory power of chrome poisoned kidneys.

Details of a very interesting case of chrome nephritis in man has been recorded by Major (103). As in animals, the lesions were chiefly in the tubules, and mainly in the convoluted tubules. Such glomerular and interstitial changes as were noted were old and patchy and evidently had existed prior to the poisoning. (The subject was a male of 59 years). The case was studied very carefully during the month that elapsed between poisoning and death, and is valuable on that account particularly. The urine had been examined and found normal on two occasions prior to the absorption of the chrome (applied to a malignant ulcer of the face.)

The urinary output was lowered at the onset, and, for the first three days there was a copious albuminuria with many epithelial and granular casts. Soon the output of urine rose, and remained above normal nearly till death, before which it fell coincidently with decreased fluid intake.

Albuminuria persisted throughout, though it fell rapidly in amount after the first three days. An attempt to work out the probable total loss of albumen by noting the actual loss on the days on which it was estimated, and plotting these out on a suitable graph suggests that the total albumen lost must have been in the neighbourhood of 50 grams. The weight of the kidneys post-mortem was 373 grams (right - 176 grams. Left - 197 grams).

There was no oedema at any time and no anasarca or ascites post-mortem. The blood urea

rose progressively after the absorption of the chrome, and was 320 mgms. per 100 c.c.s. just before death. The blood creatinin rose also. Yet, and this is very interesting, Major insists that there were never any uraemic symptoms whatsoever. It is well known that urea itself is not toxic, but it is seldom that we find clinically such a striking illustration of the fact.

Our chief interest in the case is that the results of the investigation, both clinical and post-mortem, correspond to those in experimental animals. In our own animals we, like others, have observed a progressive rise in the blood urea. It is perhaps difficult to be sure in animals that this was dissociated from a uraemic condition, but certainly we did not notice on any occasion any indication of uraemia. Convulsions were entirely absent and the lethargy during the last few days of life seemed to be due to weakness. The animals were practically unable to stand. They were emaciated, and refused food.

Since in both animals and man the lesion is preponderatingly tubular, it is to tubular damage largely that we must relate most of the effects produced.

The high blood urea may, as Shaw Dunn (153) suggested in relation to oxalates, be due to unselected reabsorption by the damaged tubular cells, which allows of the "seeping back" of urea from the filtrate into the circulation. We know that the threshold for urea (Cushny 33), though low, is not nearly as low as that for some other substances, - e.g. creatinin, and that the concentration in the blood of these other substances in nephritis is less raised and later raised than is the urea concentration, hence it is probable that the hypothetical uraemia-producing substance or substances are very low threshold bodies, and may therefore, even more than creatinin, remain at a normal level longer than urea. This would be quite comprehensible on the modern theory, because the cells of the tubules might the more tenaciously prevent the return to the blood from the filtrate of the substances of normally lower concentration in the blood. A greater degree of tubular damage might be requisite to allow of their mechanical washing back than the degree which would allow of some return of urea. Such a mechanisim might then explain the dissociation of urea retention and uraemic symptoms in such cases as these chrome ones, and the usual tendency for a sequence of raised blood urea, raised

blood creatinin, and then uraemia, in that order. At the same time, it would explain why urea retention and uraemia usually go together, for they may both at times be dependent on tubular damage and will be dissociated only until that damage has progressed beyond a certain point. There are of course other possibilities, for it is not even certain that uraemia is always due to the abnormal retention by the kidneys of chemical substances.

Some other of the clinical and biochemical features will be discussed in a later attempt to correlate the observations during life with post-mortem changes in chemical nephritis generally (p.149.).

Mercuric Chloride.

The literature up to 1904 has been collected by Lyon (95.).

Overbeck (124) commented on the appearance of albumen in the urine of patients treated with mercury, and regarded this as an indication of catarrh of the kidneys.

Pavy (127) noted the presence of extensive calcification in the tubules, without glomerular changes.

Karnoven (72), in addition to the distinctive tubular changes, claimed the production of glomerular changes.

Kaufmann (73) claimed that a capillary thrombosis occurred in all organs, and that the tubular changes were secondary to the block of capillaries. This has not been confirmed by any other observer.

Lyon (95) found no characteristic changes in the glomeruli, even when a rabbit lived 101 days, and even in the presence of extreme tubular changes. The most marked tubular lesions, and, when it occurred, the most marked calcification, were in the broad part of the ascending limb of the loop of Henle. Some, but only some, of the convoluted tubules showed similar lesions later. The collecting tubules showed debris

from higher up, and the usual phagocytic activity on such debris, but no lesions in their cells. Chronic interstitial changes were not produced, save rarely a little localised connective tissue formation around calcified areas. Around most calcified areas there was no increase of connective tissue.

Very little recent experimental work has been done with mercuric chloride.

Observers of human cases of accidental or suicidal poisoning have come to conclusions very similar to those based on animal experimentation.

Thus, Prévost (137) and Griffon (57) both found no glomerular changes.

Canuet and Pilliet (19), however, mentioned glomerular as well as tubular changes in a case described by them, but gave no detailed description of the glomerular changes.

In a case of mercury poisoning which died in Aberdeen Royal Infirmary on the tenth day, there were no glomerular changes but degenerative changes were evident in the tubules, with here and there a very little calcification in the tubules of both cortex and medulla.

There has been much discussion of the origin of the calcified material in the renal epithelium, but for our purposes it is sufficient to note it as a frequent accompaniment of the tubular degeneration caused by mercuric chloride.

The results with this substance, then, are not in all respects uniform, but are strongly in favour of a preponderatingly tubular lesion, with, no doubt, involvement of the glomeruli if the dosage be sufficiently increased. The evidence is strongly against relatively severe glomerular lesions and against the possibility of producing progressive glomerular changes or interstitial overgrowth. The tubular lesions are apparently most marked (Lyon 95) in the broad part of the ascending limb of the loop of Henle, but occur later and to a lesser extent in other convoluted tubules.

The localisation of the severer tubular damage is much as we would expect it to be on the modern view of renal function. The main lesions are in the "secreting" or active part of the loop of Henle, which is situated fairly far down in the tubule, and

at a site where normally concentration of the filtrate will nearly or actually have reached its maximum. It is scarcely Nature's custom to provide a barely adequate unit or organ, and it unlikely therefore that the average filtrate requires to be concentrated successively at each stage right down to the end of the second convoluted tubule before a balance is attained. Rather is it likely that under average conditions the balance between filtrate and blood serum is attained long before this, and that the lower cells are called into action only under special conditions, either an unusual composition of the filtrate (e.g. diuresis) or an inadequate function on the part of degenerated or atrophic epithelial cells higher in the tubules. This explains why the lesions may be as marked in the loops of Henle as further down. Why they should be more marked in the loops of Henle is less easily explained, unless we assume that in the actual process of damaging the cells of the loops of Henle, a certain amount of the mercury is fixed in these cells, so that the concentration to which subsequent cells are exposed is actually less than before. The rather later lesions in "some of the convoluted tubules" probably concern the second convoluted tubules.

Moreover, if we have the last of the reabsorption taking place in the loop of Henle, one would expect this reabsorption current to create a more intimate surface contact of the poisonous ions with the cells here than lower down, where, equilibrium being established, there would be simply a flowing past of the filtrate. Such increased intimacy of contact might be anticipated even if the mercury were amongst the substances entirely retained in the filtrate.

It is recognised that the appearances thus explained are by no means incompatible with an excretion mainly by the loops of Henle but also by other tubules, and that the explanation given does not in itself contribute anything to strengthen the modern theory, for we have certainly had to resort to supposition, though, we think, reasonable supposition, in making the explanation.

Our adherence to the modern view is based, not on this or that particular ground, but upon the superior unity of the whole theory, and upon the cogent arguments adduced from all points by Cushny (33) in its defence. We have striven, not to strengthen the theory, but to show that facts such as have frequently been brought forward as amongst the strongest arguments for another view, are not incompatible with it (the modern theory).

When applied to the lesions of chemical nephritis, the older views have a certain superficial simplicity. They claim the site of the lesion as the site of excretion of the particular substance. But this simplicity is only superficial. It is impossible, if we map out the particular excretory powers allotted to each fraction of the tubule, to discover any underlying unity, to find, for instance, any nearer chemical relation between the substances excreted at one particular point than between substances excreted at widely different sites. One is driven to assume a complexly varying adaptability of the cells at different sites to a host of individual substances. The superficial simplicity covers a deep-seated complexity, even confusion. With the modern view, on the other hand, the difficulties are chiefly in minor adjustments and become prominent in just such pathological conditions as we are studying, rather than in the explanation of physiological function, and underlying all there is a true simplicity and unity.

Altogether apart from considerations related to experimental nephritis, a study of the older views tempts one to regard them more as a surrender of all attempt to unify renal function than as a reasonable theory. To the glomeruli and to the different parts of the tubules are assigned an ever increasing number of separate and incoordinable selective powers. The modern theory demands from the renal cells a single specialised function, that of reabsorbing a fluid of definite composition from the filtrate; and in so demanding a complex but single function, places the cells in line with other highly specialised cells (e.g. glandular cells).

We therefore prefer to consider the possible explanation of individual points on the basis of the modern theory, rather than take advantage of the unscientific elasticity of the older views.

Turning to one more point in the histological picture of mercury poisoned kidneys, we might regard the patchiness of the degenerative change in the convoluted tubules as partly due to the intermittent activity of individual glomeruli. Such intermittency has been described by Cushny (33), and is in accordance with the recent views of Mackenzie as to phases of alternate rest and activity on the part of functional units. A similar intermittent activity is described by Khanolkar (75).

Cantharidin.

Amongst the earlier workers with this substance were Cornil and Brault (29). By injecting .005-.02 gram. of cantharidin subcutaneously, they claimed to find in the earlier cases chiefly glomerular lesions, of which, however, in view of later work, it is important to give some description. Little is said of alterations within the tufts. The tufts occupied only one half or even one third of the capsular space, and were compressed by an exudate in the space, in which were embedded large rounded vesicular nuclei which they regarded as belonging to swollen emigrated lymphocytes. The capsular epithelium was unaffected at this early stage, but later became swollen and was desquamated. The convoluted tubules then showed swelling and degeneration and there was granular debris in their lumens. Later the capsular space cleared, but capsular lesions were still evident.

Browitz (15) found enlargement of the glomeruli, but otherwise a picture similar to the preceding, save that the exudate in the capsular space was granular and contained no definite nuclei.

Eliaschoff (45) found changes similar to those described by Cornil and Brault. Again the cells in the capsular spaces were interpreted as emigrated white blood cells, but again it was noted that they were greatly swollen.

Welch (170), using white rats, found proliferation of the epithelium of the glomerular tufts in some cases. In other cases there was more proliferation of the epithelium of the "parietal" aspect of the capsule. In acute cases, cells were sometimes found in the capsular spaces, and these were interpreted as being secreting epithelial cells. Our experience with rats has been that the minor proliferative changes Welch describes in the glomeruli cannot safely be taken as due to the injections.

None of the above writers have claimed to have produced even by repeated injections any consequent or significant degree of interstitial change. Aufrecht (3) claimed by repeated injections to have produced an interstitial nephritis in one animal, but failed with another also injected over a prolonged period.

Austin and Eisenbrey (4) assumed cantharidin to produce mainly glomerular changes, and used it as a glomerular poison in the study of the "vascular response" of the perfused kidney. Yet all they describe in the glomeruli is congestion.

Lyon (95) agreed with prev-ious writers as regards the usual absence of interstitial changes, and described such changes, where they occurred at all, as consisting of a slight localised collection of lymphocytes around dilated veins. He clarified the picture remarkably in other respects, however. He recorded appearances in the capsular space similar to those described by previous observers, but interpreted them quite differently. Along with the large cells in the capsular space, he invariably found marked swelling and degeneration in the convoluted tubules and especially in the bread part of the ascending limb of the loop of Henle. Even the collecting tubules were affected in the cases dying earliest. Many of the tubules were choked with swollen disintegrating cells with large pale nuclei, and this choking of the tubules was by him considered to have caused a damming back of catarrhal secreting cells into the capsular spaces. The cells in these spaces he regarded therefore as derived from the tubules, and thus got rid of the anomaly of profuse emigration of leucocytes from relatively normal tufts. His microphotograph abundantly confirms his view as to the origin of these cells, and it seems that previous workers had probably been misled by the site of the cells. It will be remembered that both Cornil and Brault and Eliaschoff noted that the "emigrated" cells were very large and swollen, although they did not apparently appreciate the significance of this fact.

Lyon did not always find the glomeruli altered, and the changes, when present, were slight and consisted of slight congestion and polymorphonuclear infiltration.

Thus, apparently, one of the so-called "glomerular" chemical poisons is really predominantly tubular, and, as is the case with other poisons, most have failed to produce with it either progressive glomerular lesions or increase of the interstitial tissue.

Once more, also, the tubular lesions concern the more active cells, the so-called "secreting" cells, and, according to Lyon, mainly the ascending limb of Henle's loop, a selective localisation that has already been discussed in dealing with mercuric chloride. It is doubtful if many writers who describe lesions in "some" of the convoluted tubules, in addition to those in the loops of Henle, have differentiated between the first and second tubules, and it may be that the tubules they

refer to as affected are chiefly second convoluted tubules.

Even where a differentiation is attempted, it is difficult to be quite sure of the identity of all the tubules. Testuté's Anatomy places the second convoluted tubules largely in the subcapsular zone, but other parts of it lie, he says in the deeper parts of the cortex, with the glomeruli, the loops of Henle and the first convoluted tubules. The only distinction between the two convoluted tubules where they lie together is, he thinks, a rather fainter staining of the cells of the second convoluted tubule.

Aloin.

Kohn (81) described degeneration and necrosis in the tubular epithelium from the administration of aloin. Repeated administrations failed to cause interstitial changes. Murset (109) similarly found the tubular degenerative changes to be the chief ones, but claimed to obtain areas of cellular infiltration and commencing atrophy of the tubules (spontaneous?) with increase in the connective tissue. Cushny (33) noted the drug amongst those which might in certain animals inflict damage on the kidneys. The reason for the effect being on certain animals alone is, he says, that in these there is a greater excretion of the drug by the kidneys. In man, in dogs, and in cats. purgation is the chief result and renal lesions are absent, very little of the drug being excreted in the urine. In the rabbit, no purgation results, but renal lesions are produced, there being apparently greater excretion in the urine.

The lesions are tubular, Cushny adds, consisting of necrosis of the secreting epithelial cells, and, if the dose is sufficient, death results in a few days.

Borax.

Borax was claimed by Harrington (58) to produce in cats both tubular and interstitial changes. Some of the animals were allowed to live for 133 days. We have noted no further work with this substance.

Oxalates.

The action of oxalates on the kidney was first noted by Kobert and Küssner (80), who related the anuria produced to blockage of the medullary tubules by oxalate crystals. Fraenkel (51), however, pointed out that the tubules might be loaded with crystals although during life there had been no anuria. Murset (108) describes swelling of the glomerular and capsular epithelium, and albuminous exudate in the capsular spaces; but the more marked changes were in the tubules, especially in the broad parts of the ascending limb of the loop of Henle. Ebstein and Nicolaier (44) observed similar changes, but failed in an attempt to produce granular contracted kidneys. More recently Shaw Dunn (153) has given a detailed account of the pathology of oxalate nephritis. He described the constant production of a tubular nephritis, the lesions being most marked in the latter part of the first convoluted tubules, but present to a lesser degree in other "secreting" tubules. The lesions were patchy, severer changes being present in some tubules than in others of the same type. Shaw Dunn explains this by suggesting that the bulk of the oxalate was excreted within a few minutes (- the intravenous method of administration was used), and that consequently only the particular tubules active during that brief period were severely affected. He considers that the results accord with the modern theory of renal function, in that a considerable concentration of the oxalate will have been attained by the time the lower parts of the first convoluted tubules have been reached. Of the poisons so far noted, however, this seems to be the one whose selective site of action is most difficult to explain on that theory. It may be, of course, that the rapidity of excretion noted by him (and natural when the intravenous method was used) made the concentration in the actual filtrate so high that very little subsequent absorption was required before the concentration was raised to a degree capable of causing damage. The same reasons as were advanced in dealing with mercuric chloride, might explain the lesser degree of the damage lower down (fixation of oxalate in the damaged cells).

The glomerular changes consisted in the transudation of a little albuminous material, congestion, and sometimes haemorrhages, but no marked changes. He considered, however, that in the earlier stages there was a glomerular stasis.

With repeated doses, the lesions remained mostly tubular, and chiefly still in the lower parts of the first convoluted tubule. Glomerular changes were not produced, and the only significant interstitial change was a very considerable oedema which, he thinks, may have influenced function by compressing the vessels and so diminishing the glomerular filtrate.

It is interesting to note that in two experiments in which dead haemolytic streptococci were used in conjunction with oxalate, much more marked glomerular changes were produced.

Progressive urea retention was noted in the animals subjected to repeated doses, and was attributed to a failure of the damaged tubular cells to form a barrier against reabsorption of the filtered urea.

The excretion of water was only temporarily diminished and sometimes not markedly. Later, there was always polyuria. On the modern theory, this conforms to the histological appearances. The temporary glomerular stasis would diminish the glomerular filtrate markedly at first, but this would soon pass off, and would be rapidly more than counterbalanced by inadequate reabsorption by the impaired tubular cells (polyuria).

Even more recently, oxalate nephritis has been produced by Browne (16), to whom, however, the production of nephritis was simply a preliminary to the study of placental infarction and abortion. His results confirm those of Shaw Dunn. The lesions found were mainly tubular, and were chiefly in the first convoluted tubules. The glomeruli were swollen and congested, but no further change was noted in them. Widespread oedema was seen in the interstitial tissue, and in some cases there was focal increase of interstitial tissue, which, however, judging from his microphotographs, is indistinguishable from that occurring in spontaneous nephritis.

The blood urea was rapidly elevated after each injection of oxalate and often fell just as rapidly between doses.

Tartrate.

F.P.Underhill, H.G. Wells and S. Goldschmidt (162) produced a tubular nephritis with this substance. The lesions were mainly in the convoluted tubules (which

part is not stated), and to a lesser extent in the loops of Henle. The collecting tubules escaped. Vacuolation followed by necrosis of the epithelial cells was observed, with the gradual formation of casts from the tubular debris.

The urea retention was marked, chloride retention slight.

Whilst effects were best produced by injection, they could also be obtained by heavy dosage with Rochelle salts by the mouth, a fact which they interpret as a warning against the over-generous use of such salts therapeutically.

They quote Baer and Blum as having noted in 1907 that the subcutaneous administration of tartrate could prevent the subsequent development of phloridzin glycosuria (as many tubular poisons do.)

Uranium.

The action of this substance on the kidneys has been repeatedly investigated. The main conclusion is clear. Its chief influence is on the tubules, but it produces some degree of degenerative change in endothelium, and this is naturally noted mostly in the glomeruli, although we have found no evidence that its action is confined to the endothelium there. On other points, however. the evidence is conflicting. Some claim to have succeeded in producing progressive glomerular changes, but others have failed to do so. Again, though some have obtained increase in interstitial tissue, especially with repeated doses, others have failed to do so. The literature will then have to be examined chiefly to determine what support there is for these claims. It is all the more difficult to decide on these points because practically all writers admit that definite, though slight, changes in the glomeruli are produced in early stages. In this, uranium would appear to differ from previous poisons considered, and so we have to investigate the possibility of progressive glomerular changes particularly carefully here.

Christian and O'Hare (23) were the first to describe the presence of peculiar hyaline droplets in the endothelium of the glomerular capillaries. They noted ,too, proliferation of that endothelium, thrombosis, haemorrhages into the tufts. distension of Bowman's space

with granular material, and occasionally proliferation of the "parietal" epithelium of the capsule. This was in addition to the marked tubular lesions on which all are agreed. In so far as regards the hyaline droplets in the tuft endothelium, all subsequent observers are agreed that it does appear in a certain proportion of cases, and is therefore typical of uranium poisoning.

In a later paper, however, Christian, Smith and Walker (22) claim to have induced chronic lesions in rabbits and guinea pigs by giving repeated doses of uranium nitrate (or potassium bichromate), and of these results particularly we feel doubtful. They claim that round celled infiltration and increase of connective tissue develop, forming foci of triangular shape on section, the base of the triangle being at the cortical surface, the apex running inwards. In such areas the tubules are destroyed, but the glomeruli are relatively little involved. As was pointed out by Leiter (88) the lesions thus described are in type strictly comparable to those of spontaneous nephritis, and are not, in any case, the result of a progressive glomerular nephritis.

Christian's work is, however, corroborated by some other observers. Dickson (40), using guinea pigs and, later, rabbits and dogs, and giving small doses of uranium nitrate subcutaneously over prolonged periods, found on examination dilated "cystic" glomerular tufts, thickening and hyaline degeneration of Bowman's capsule, with fairly diffuse round celled infiltration but no fibrosis. Where, however, he had given an initial larger dose sufficient of itself to produce an acute nephritis, and had followed this up by repeated smaller doses, he found that new connective tissue developed, with new elastic tissue in Bowman's capsule, and some dimpling of the surface of the kidney. Though he describes rather more glomerular, or at least peri-glomerular, change in the later experimental animals, the changes are still comparable to those in spontaneous nephritis, and very like those we have found in two of our rabbits (microphotographs 11 & 12), changes which we believe to have been spontaneous.

Boycott and Ryffel (13), in 1912, summed up the evidence to date, and regarded it as in favour of uranium being predominantly a tubular rather than a glomerular poison.

Baehr (6) in only one of eleven animals injected subcutaneously with a single small dose of uranium nitrate, found adhesions of the glomerular tuft to the capsule, albuminous exudate, and epithelial

crescents. In eleven rabbits in which uranium was injected directly into the renal artery, extensive glomerular lesions were produced, and the glomeruli were described as showing successively - coagulation necrosis of the capillaries, growth of capsular epithelium to form a syncytium, secondary canalisation of the glomerular mass by new capillaries, and hyaline changes in the tuft with adhesions to the capsule. Up to about half the glomeruli were affected in some cases.

These are certainly striking changes, far more so than any produced by other workers with uranium, and their special method of injection seems to be responsible. Injection into the renal artery must have meant almost immediate and intimate contact of a high concentration of uranium with the glomerular capillaries, much higher than could have been secured by the introduction of any ordinary dose into the general circulation. Whilst, therefore, the experiments suggest a possible method of producing marked glomerular changes, the same author's previous experiments with subcutaneous doses tend to confirm the view that the action is not selectively or strongly glomerular.

Weisel and Hiss (169) claim, by using uranium nitrate intraperitoneally and adrenalin subcutaneously, to have produced glomerular swelling, with haemorrhage and exudation into the tuft. In later stages, they noted proliferation and organisation in the tufts, with subsequent contraction. Eventually, they state, contracted kidneys resulted. This is the only paper which claims that a sequence of progressive glomerular changes has been produced, leading finally to contraction of the kidneys.

Roth and Bloss (146) seeking to confirm the work of Weisel and Hiss, used uranium and adrenalin by the same methods, but obtained chiefly tubular changes, although in a quarter of the animals they noted the presence of the hyaline droplets in the endothelium of the glomeruli reported by others.

MacNider (100) says that his results agree with those of Dickson. He claims to have produced an increase of cellular connective tissue between the tubules, marked proliferation of connective tissue cells within the glomerular tufts, obliteration of many capillary loops, great thickening of the glomerular capsule, and cellular fibrosis around the glomeruli, in addition to the marked tubular changes.

Pohl (134) quoted by Cushny (33) described a pure tubular nephritis as the result of repeated doses with uranium. The characteristic feature was marked polyuria with slight albuminuria. The epithelium of the tubules was necrosed or entirely stripped off, leaving the basement membrane exposed.

Nuzum and Rothschild (112) gave a number of rabbits repeated small injections of uranium nitrate, the average duration of life after the first injection being 132 days (74 - 175 days). In all cases without exception, the tubular changes were marked, and in type corresponded very closely with those we have found in rabbits subjected to repeated chrome injections (degenerative, necrotic and atrophic changes of various kinds).

The changes in the glomeruli, on the other hand were inconstant. Frequently there was proliferation of the glomerular endothelium, thickening of Bowman's capsule and a little round celled infiltration surrounding the glomeruli.

Between the tubules, and especially round small bloodvessels, there was sometimes a little round celled infiltration. These are changes of slight degree, and similar to those we have found in chronic chrome poisoning. They do not seem to indicate either a progressive glomerulo-nephritis, or even changes of a degree sufficient to encourage the hope of producing such by further injection. The nephritis remains a predominantly tubular one. Moreover, the slight glomerulo-interstitial changes produced were inconstant.

This moderate degree and dubious type of change found by recent workers in the attempt to confirm earlier work which claims to have produced much more marked changes tends to weaken rather than support the earlier conclusions. Nuzum and Rothschild prolonged their experiments over a period much longer than some of their predecessors considered necessary for the production of marked chronic changes.

Leiter (88) is inclined to believe that the only changes proved are the tubular, and, frequently with, in addition, the peculiar hyaline droplets in the glomerular endothelium described by many writers.

We are inclined to agree with this sceptical verdict. Support for it is available in the experiments of Christian already described. In these, interstitial lesions are described as invariable, but one must make two comments on this point. As we have already said, the lesions are of the type of spontaneous nephritis.

The second comment is that Christian performed similar experiments with potassium bichromate and obtained exactly similar results. We have been unable by repeated injections of bichromate over periods as prolonged as those in Christian's experiments to induce any significant degree of interstitial change.

We are consequently all the more disposed to regard Christian's rabbits as having probably suffered from spontaneous nephritis, although the "spontaneous" infection of the kidney may, as already suggested, have been predisposed to by the injections.

We therefore regard the direct production by uranium of progressive glomerular or interstitial changes as unproven, and, indeed, very unlikely. There is, however, apparently a little more tendency with it than with other chemical poisons yet reviewed to attack the glomerular endothelium in the early stages as is demonstrated by the frequent detection of hyaline droplets in that endothelium. The degree of these early glomerular changes is, however, insufficient to determine the onset of progressive alterations in the tufts.

Thallium.

Dal Collo, in an article abstracted in Medical Science (35) reported the results obtained by injection of thallium into rabbits, rats and guinea pigs. In rabbits, he produced lesions of the second convoluted tubules, and in guinea pigs and in rats other tubules as well sustained damage. He described also production of numerous capillary haemorrhages, not confined to the glomerular tufts.

He considered that the changes were analogous to those in chrome poisoning, and with this we are inclined to agree.

The distribution of the tubular lesions is apparently explicable by simple reabsorption of fluid from the tubules, and consequent gradual concentration of the poison.

The abstract does not refer to the condition of the loops of Henle.

Monobasic Sodium Phosphate.

Hirsch (65) by subcutaneous injections of the above-named substance obtained necrosis of the cells of the convoluted tubules and loops of Henle. Again the nephritis is apparently tubular and the mechanism of concentration by reabsorption is probably at work in its production.

His suggestion that the clinical, oral, administration of phosphates to man may lead to renal damage is not necessarily a correct deduction; there being no evidence extant that by oral administration in animals a nephritis can be produced.

Uric Acid.

Shaw Dunn (154) recently described a nephritis produced by intravenous injection into rabbits of doses of one half to one gram of uric acid per kilo. of body weight.

The nephritis was a tubular one, and affected chiefly the parts of the "secreting" tubules where uric acid becomes concentrated - the broad part of the ascending limb of the loop of Henle, and the second convoluted tubules.

The collecting tubules showed patchy injury but only where the epithelium was in contact with actual solid urate in the lumen. As with oxalate, Shaw Dunn got a raised blood urea with this apparently purely tubular nephritis.

He did not succeed in producing chronic changes.

Lead.

Most experiments with lead have been with the purpose of producing chronic interstitial nephritis by repeated injections. There is, however, little doubt that an adequate single dose can produce acute tubular changes. Ramondi (139) quote by Ophüls (117) claimed

to have produced a commencing chronic nephritis by administering lead to guinea pigs. Charcot and Gombauld, quoted by Cornil and Brault (29) described as resulting from chronic lead poisoning in guinea pigs areas of atrophied tubules, in which, later, replacement fibrosis followed. The vessels and glomeruli were only slightly affected, and what effect there was in these was secondary, they thought, to the tubular changes.

Ellenberger and Hofmeister (46) claimed to have produced diffuse nephritis in sheep.

Coen and d'Ajutolo (27) quoted by Ophüls, could get only small areas of round celled infiltration, and no further interstitial change.

Prévost and Binet (138) failed to produce chronic lesions in guinea pigs with lead acetate, but vaguely claimed "marked renal changes" with lead carbonate.

Both Oliver (116) and Sueglitz (158) found only insignificant areas of cellular infiltration in the later stages.

Annino (2), quoted by Ophüls (117) is another who found no interstitial changes.

Oppenheim (120) and Jores (68) also failed, though the latter's experiments all lasted over two months, and in one animal over 14 months.

Both Hirsch (64) and Paviot (126), however, succeeded in producing some interstitial change in prolonged experiments.

Lyon (95), using rabbits, found no significant changes.

Ophüls (117) used repeated injections of lead in guinea pigs and dogs. The guinea pigs showed only unimportant changes. In dogs, he maintains that he produced a marked chronic interstitial nephritis without arterial sclerosis. He does not describe a true glomerular nephritis.

Using rats, we have failed to produce significant interstitial or glomerular changes by repeated injections of lead over prolonged periods (p 139-143).

Such conflicting results, taken along with the known fallacy (spontaneous nephritis), may fairly be held to throw doubt on the possibility of the production of true chronic interstitial nephritis by lead.

One feels that possibly the clinical evidence on which the primary assumption of such an action of lead was based, consists of two main facts, both true, but, even taken together, quite insufficient to indicate that lead can produce chronic interstitial nephritis.

Firstly, it is true that lead may cause some albuminuria, and probably, as in the case of the other chemical poisons, this is due to a tubular lesion produced when a sufficient dose is administered.

Secondly, it is apparently true that lead may cause arterial sclerosis, but it is well known though so far unexplained that the distribution of arterio-sclerotic changes varies widely, and that a widespread arterial sclerosis does not necessarily affect the smaller vessels at least of the kidney.

Klotz (79) believes that sclerosis of the main renal artery, and of the branches of the artery are quite different in type, and often do not occur together. The former is the only type which occurs as a part of a true primary arterial sclerosis, and it is of no clinical importance. Sclerosis of the smaller branches, on the other hand, occurs in nephritis, without probably being the cause of it, and is therefore associated with all degrees of renal insufficiency.

Author's Experiments with Chemical Poisons.

Animals used.-

The animals used were rabbits and rats. The majority of the experiments were performed with rabbits. The choice was partly influenced by the ease with which abundant urine could be collected, partly by the more convenient size of the animal, and partly because the rabbit is one of the few animals in which the detection of fat in the kidney by the usual staining methods may be regarded as definitely pathological (Lyon 95.).

All animals used were apparently vigorous and in good health when the injections were commenced.

Diet.-

All animals were on a diet of fixed type, but no attempt was made to regulate the quantity consumed.

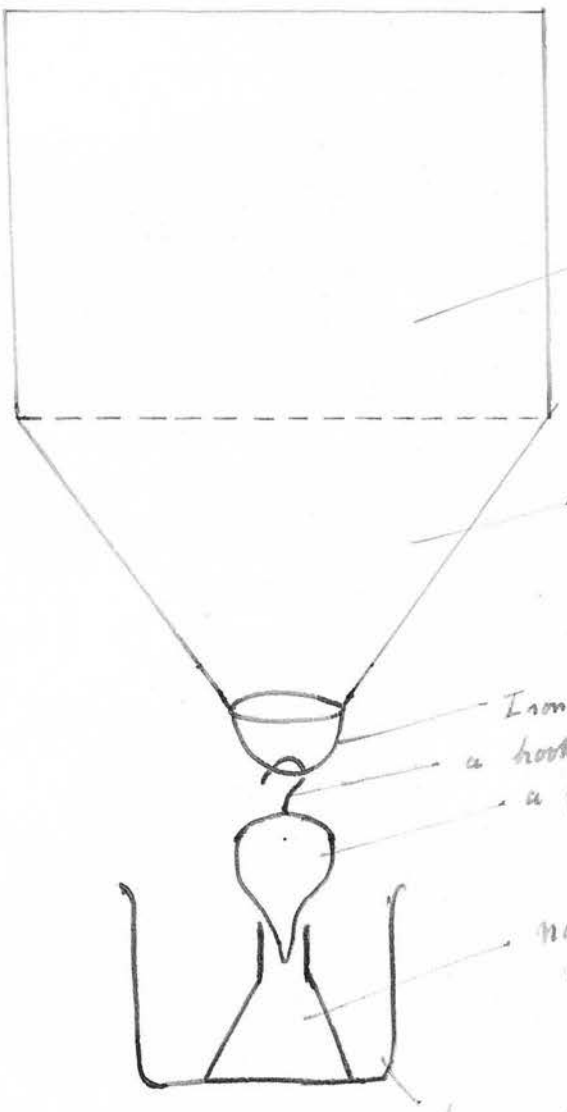
The rats were given bread and milk, alternatively with oats. Occasionally about once weekly, meat (rabbit) was added.

The rabbits were fed on green vegetables, with oats instead ever third day. If an animal was seen in the course of injections to be off its food, a dish of water was put into the cage. Under such circumstances, it frequently drank quite greedily.

The Cages.-

As far as possible, the usual type of special metabolic cage was used (Baird & Tatlock Catalogue P.351 & P.351A). These were of a size suitable for a rat or a small rabbit, and it was partly in order to get as full use as possible of these cages that small young rabbits were used as frequently as possible. These metabolic cages are constructed so as to collect urine quantitatively and free from faecal contamination. This is achieved by means of a device easily understood by reference to the accompanying sketch.

When a rabbit was too large for the special cages, ordinary large cages were provided with bottoms of perforated zinc (perforations 1.3 cms. x .7 cm. at .4 cm. intervals.)


Cage with perforated floor.
Funnel down which excreted materials fall.
Iron ring, to which is attached, by
a hook,
a pear-shaped glass bulb.
narrow-necked flask into which
narrow end pear-shaped bulb
dips, the flask consequently
catching the urine.
large glass container, which catches the
faeces.

and the urine was allowed to drain into a large white-enamelled tray on which the cage was set. After collection of the urine, all parts of the cages were thoroughly cleaned daily.

The Urine.-

The urine of all animals was examined, usually on several occasions, before injections were commenced. A small number of the rats showed a very faint trace of albuminuria with the boiling test before injection. Yet it was only very rarely that a trace was noted with the nitric acid test, or that anything abnormal was discoverable microscopically. On further investigation of this point, it was found that the supernatant fluid, after water had been shaken up with some of the bread used in feeding the animals, gave a similar slight haze to the test. As there was some opportunity for a similar contamination of the urine, which might then stand up to 24 hours with the breadcrumbs lying in it, it was concluded that the fallacy probably arose in this manner, and the boiling test was therefore, though done as a routine, not seriously considered in the case of rats and we have not therefore recorded the results.

Turning to the rabbits, none showed any abnormality of the urine before injection. An old hare, used in one experiment, showed a distinct trace of albuminuria. It was used in an acute experiment, and histologically the kidneys showed evidence of slight chronic change as well as of acute alteration (Hare I p.). All the rabbits were young animals.

The twenty-four hour urine of every animal was collected every day, and when possible was measured (i.e. when the metabolic cages were used.)

It was examined daily for albumen by the ordinary boiling and nitric acid tests, and where there was any doubt, by the salicye-sulphonic acid test in addition.

The sediment, not centrifuged, was then examined microscopically for cells. casts etc.

When albumen was present in sufficient quantity it was estimated by use of the Esbach tube.

Sometimes the urea concentration test, using the Doremus tube, was applied, but, as urea was not usually administered beforehand, this was not regarded as important.

Blood urea estimations, when made, were performed by the urease method (Maclean 98). The blood for such estimations was obtained from the ear vein.

All the rabbits, and most of the other animals, were weighed at the commencement of the experiment. Post-mortem, the kidneys were weighed in all cases and the spleen almost always, and a complete post-mortem examination was made in every case.

Fixation of Organs, etc.

Zenker's solution and Pick's formalin and salts solution were used in duplicate at first, but the difference in results was not apparently great from our point of view, and the greater part of the work was carried out with the formalin solution alone.

Both frozen and paraffin sections were prepared in all cases.

The frozen sections were stained with (watery solution of) haemalum, and picrofuchsin or eosin; sections were also stained for fat with Herxheimer's Scharlach R solution (63) modified by the addition of a small amount (one third the amount of Scharlach) of Sudan III (Shennan). The solvent in this solution consists of equal parts of acetone and 70% alcohol.

Occasionally sections were stained with Nile Blue Sulphate A or other stains.

Paraffin sections were stained with haemalum, others were stained with 1/2% watery haematoxylin by the iron alum method (Heidenhain's 60) and were counterstained with eosin or fuchsin.

Other stains were used occasionally.

Control Rabbits.

Five healthy uninoculated rabbits were killed at various times, and their kidneys were examined as controls. They showed no pathological changes and no evidence of spontaneous nephritis. They showed, however, a rather larger number of round cells in the tufts than might have been looked for, and this was

accordingly allowed for in estimating pathological changes in the inoculated animals.

(No fat was found in the kidneys of any of these control animals).

Control Rats.

Five control rats were used.

The picture was that which one would, from experience with human and rabbit kidneys, expect in normal animals, with the two exceptions now detailed.

1. The glomerular tufts were often what one would have been inclined to call a little overcellular. There were quite a few infiltrating small round cells, and in one or two cases there was also a commencing development of connective tissue within the tufts.

In two cases a small number of polymorphs, usually one, was found within some of the tufts.

(The glomerular nuclei always stained well and were not swollen, nor was there any damage to the glomerular epithelium, any debris or other matinal in the capsular space, or any adhesion of the glomerulus to the Bowman's capsule.)

2. In some cases the tubules showed considerable raggedness of the luminal edge of the epithelial cells, lining many of the convoluted tubules, and there was consequently at times quite a distinct amount of debris in the lumen of some of the convoluted tubules.

(No fat was found in any of these control rat kidneys).

N. B. THE PROTOCOLS OF THE VARIOUS EXPERIMENTS WHICH IMMEDIATELY FOLLOW THIS, AND OF OTHER EXPERIMENTS LATER IN THE SECTION, ARE NECESSARILY FAIRLY LONG, BUT AT THE END OF EACH IS GIVEN A FAIRLY BRIEF SUMMARY OF THE CHIEF CONCLUSIONS.

Experiments with Pottassium BIchromate.

Animals used.
Rabbits C, D, E, F, V, 9,
Rats 14, 15.

Rabbit C.

Healthy rabbit. Weight 1470 grams.
Urine before injections, (5 examinations), nil abnormal chemically or microscopically. Average quantity 40 c.c.s daily.
23/3/26. Fasting Blood Urea. 25 mgms. /100 c.c.s.
24/3/26. 9.45 a.m. 3/160 gram. Pot.bichrom. in water intraperitoneally.
25/3/26. Urine 7 c.c. Albumen doubtful to HNO_3 test; distinct trace to boiling test.
Micro:- One or two epithelial cells; no casts.
10.30 a.m. 1/40th gram. Pot.bichrom. in water intraperitoneally.
26/3/26. Urine 2 c.c. Albumen positive to nitric acid and boiling tests. Micro:- Hyaline casts: one or two granular casts: a few epithelial cells: a few R.B.C.
11 a.m. 1/40th gram. Pot.bichrom. in water intraperitoneally.
27/3/26. Urine 4 c.c. Albumen distinct quantity to both nitric acid and boiling tests. Micro:- Numerous granular, some hyaline, casts: numerous epithelials.
9 a.m. Blood Urea 65 mgms. /100 c.c.s.
11 a.m. 1/40th gram. Pot.bichrom. in water intraperitoneally.

29/3/26. Urine (2 days) 2 c.c.s. Albumen present to nitric acid test. Micro:- Numerous granular and some hyaline casts: numerous epithelial cells and R.B.C.
Found dead but warm this morning.
P.M.

Right kidney large: surface pale. Capsule strips readily. The cut surface exudes watery fluid and shows a pale cortex with lines and spots of apparent haemorrhage. Medulla congested. Weight, 7.7 grams.
Left kidney, appearaances similar. Weight 7.48gms.
$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{15.18}{1470} = .010$. (average ratio in controls= .008 - from .007 to .009).

Spleen .5 gram. pulp soft, red, almost diffluent.

Liver congested, with opaque mottling; cloudy swelling ?

Microscopic examination:-

Liver

Congestion: rather faintly staining nuclei: no necrosis: changes not comparable in severity to those observed in the kidneys.

Spleen

Sinuses distended with R.B.C. Otherwise fairly normal, save for a fair amount of brownish pigment (chrome ?) chiefly in mononuclears: reticular cells prominent: Malpighian bodies fairly prominent also.

Kidneys

The glomeruli and glomerular spaces were distended. The tufts were intensely congested and showing perhaps a little infiltration with lymphocytes. The endothelial cells were very slightly swollen, but there were no further changes within the tufts.

In only one or two capsular spaces was there a little albumen. The epithelium covering the tufts was irregular in size and some of its nuclei showed commencing karyorrhexis or partial chromatolysis, but the epithelium was absent in very few places only.

There was thus only a moderate change in the glomeruli and their covering epithelium. There was congestion of all vessels throughout the organ.

No distinct interstitial change was present, save for a little patchy round celled

infiltration here and there in relation to bloodvessels.

Many of the cortical tubules were completely necrotic. They stained uniformly pink with eosin, they showed no nuclei, and simply formed a swollen, granular, almost homogenous mass completely filling the tubule.

Such tubules had a patchy distribution. As far as can be made out, they comprised the latter part of the first convoluted tubules, and in rather less degree the broad parts of the loops of Henle, and the second convoluted tubules.

The only part of the active epithelium which pretty constantly escaped this wholesale necrosis was the early part of the first convoluted tubules. Here the tubular lining epithelium was still evident as such. Sometimes it was fairly healthy just as it left the tuft (though often containing a hyaline cast). At other times the nuclei showed some degree of chromatolysis or there was a little catarrh.

The collecting tubules, both in the cortex and medulla, and, indeed, the great majority of the tubules in the section which were not filled by necrotic epithelial cells, contained hyaline casts.

Fat:- Fat was present in the cells lining many convoluted tubules in quantity varying from a rather coarse dusting of the cytoplasm up to complete replacement of the cell by fat. Some convoluted tubules, however, showed no fat. The thick parts of the loops of Henle also contained fat.

The collecting tubules showed much less fat; nevertheless, fat was present in some of them. A few only of the numerous casts in the convoluted tubules were fatty. There was also marked deposition of fat in the interstitial tissue between the tubules both of cortex and medulla, and fat was present in small quantities in the basement membrane around some of the glomerular capsules.

There was a trace of fatty change in one or two individual loops of a very few glomerular tufts.

Summary.

Severe tubular and slight glomerular changes.

Insignificant interstitial changes.

Microphotographs 1 and 2 (l.p. and h.p.).

Rabbit D.

Healthy rabbit. Weight 900 grams.
Urine before injection (4 examinations), nil abnormal chemically or microscopically.

2/4/26. Blood Urea 18 mgms. /100 c.c.s.

3/4/26. 10.30 a.m. 1/80th gram. Pot.bichrom. in water intraperitoneally.

5/4/26. Urine 150 c.c.s. (2 days) Albumen negative to boiling and nitric acid tests. Micro:- No cells. no casts.
3 p.m. 1/80th gram. Pot.bichrom. in water intraperitoneally.

6/4/26. Urine 15 c.c.s. Albumen very faint trace to boiling and nitric acid tests. Micro:- No cells, no casts.
10 a.m. 1/80th gram. Pot.bichrom. in water intraperitoneally.

7/4/26. Urine 60 c.c.s. Albumen definitely positive to both boiling and nitric acid tests.
Micro:- Numerous granular casts, a few epithelials.
Esbach nearly 1 gram per litre.
9.45 a.m. 1/160th gram. Pot.bichrom. in water intraperitoneally.

8/4/26. Urine 42 c.c.s. Albumen positive to nitric acid and boiling tests. Micro:- No cells, numerous granular casts.
Esbach 3 grams. per litre.

9/4/26. Urine 20 c.c.s. Albumen positive to nitric acid and boiling tests. Micro:- A very few cells, numerous granular casts.
Esbach 3 grams per litre.
9.40 a,m. Blood Urea 138 mgms. per 100 c.c.s.

10/4/26. Urine 14 c.c.s. Albumen positive to nitric acid and boiling tests.
Esbach 1/4th gram per litre. Micro:- A fair number of epithelial cells, a large number of hyaline and granular casts.

11/4/26. Had died during the night. There was no urine in the container, but microscopically a few drops of urine from the bladder post-mortem contained apparently no casts but some epithelial cells and leucocytes.
P.M.
Right kidney 5.27 grams. Left kidney 5.01 grams.
Kidneys / Body Wt. = 10.28 / 900 = .011. Both kidneys especially in the medulla, oedematous.

Spleen
Soft .35 grams

Liver
Congested and pigmented.

2 c.c.s. of pericardial effusion were present. The fluid was fairly clear, but coagulated firmly soon after withdrawal. Microscopically, it contained many polymorphs, but no organisms were demonstrated.

Microscopic examination.

Spleen

The Malpighian bodies were moderately prominent, and the walls of the central arterioles appeared to be slightly thickened, whilst the finer fibrous trabeculae of the pulp were a little more prominent than might have been expected. The endothelial and reticular cells were numerous and prominent.

Liver

Cloudy swelling and some (chrome ?) pigment in a few polygonal cells.

Kidneys

The glomeruli were not congested. The absence of congestion brought the nuclei closer together and made the tufts appear overcellular, but there was no real overcellularity. A few of the endothelials of the tufts showed distinct karyorrhexis, others pyknosis. The parietal epithelium of the capsule was swollen, and in some cases showed a little proliferation (2 layers). The tuft epithelium was at parts defective, at others slightly swollen. In some of the capsular spaces there was a little albuminous material. Surrounding the afferent arterioles, there was a distinct, though small. amount of round celled infiltration along with some fibroblasts.

No increase of connective tissue was noted in the cortex generally, and no oedema.

There was a slight cellular infiltration in the boundary zone, particularly about the vessels, which were greatly congested.

In the convoluted tubules of the cortex, there was some swelling of the lining epithelium with commonly pallor of nuclei and sometimes karyorrhexis, or pyknosis. In some of the tubules there was partial or complete necrosis of the cells and some catarrh.

There was vacuolation, catarrh and necrosis of cells in the broad part of the ascending limb of the loop of Henle, whilst many spaces, apparently the remains of such tubules, had apparently lost all their epithelium.

Casts were present in some tubules in the medulla, and in dilated collecting tubules in the cortex.

Summary.

The organ thus showed a change, which, though partly glomerular, was predominantly tubular.

Rabbit E.

Healthy rabbit. Weight 1050 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.
5/5/26. Blood Urea 20 mgms. /100 c.c.s.
11.30 a.m. 1/320th gram. Pot.bichrom. in water intraperitoneally.
6/5/26. Urine 31 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- No cells, no casts.
4 p.m. 1/320th gram. Pot.bichrom. in water intraperitoneally.
7/5/26. Urine 75 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- One or two epithelial cells, no casts.
11 a.m. 1/320th gram Pot.bichrom.in water intraperitoneally.
8/5/26. Urine 30 c.c.s. Albumen negative to boiling test, trace to nitric acid test.
Micro:- No cells, no casts.
11 a.m. killed.
P.M.
Right kidney 3.8 grams. Left kidney 3.9 grams.

$\frac{\text{Kidney}}{\text{Body Wt.}} = \frac{7.7}{1050} = .007.$

The kidneys were rather pale, but there was a little congestion of the cortex.

Spleen .5 grams. Liver normal.

Microscopic examination.-

The Spleen and Liver showed hardly any alteration.

Kidneys

The glomerular changes were very slight. There was no increased cellularity, and there was no alteration in the endothelium. The epithelium, parietal and visceral, of the capsule was sometimes a little swollen and prominent. At occasional points the visceral layer was being detached or had even been lost. Here and there there were very slight indications of proliferation of the parietal layer. No coagulated albumen was to be seen in any of the capsular spaces.

The tubules showed very distinct changes, though not so marked as in the other chrome kidneys. The ducts of Bellini and some of the collecting tubules contained casts and there were occasional slight nuclear deformities in some of the lining cells of the collecting tubules.

In the convoluted tubules, and in the wider part of the ascending limb of the loop of Henle, the nuclei

of some of the cells stained fairly well, but there was a good deal of chromatolysis. some karyorrhexis, and. more commonly, some pyknosis, the changes being least marked in the first convoluted tubule and most marked in the loop of Henle. In these loops particularly the tip of the cell had sometimes disappeared, so that the small (pyknotic)nucleus actually bulged into the lumen. Sometimes, this projecting portion of the nucleus stained more faintly than its deeper parts.

The lumen of some of the convoluted tubules contained a little granular debris and in a number there was some catarrh; in some of the loops of Henle there was considerable catarrh.

Fat:- No fat was found anywhere.

Summary.

The experiment provides a clear illustration of the purely tubular distribution of the lesions in chrome poisoning with smaller dosages. The"tubules" in this sense include the invaginated capsular portion, and therefore the glomerular epithelium.

Rabbit F.

Healthy rabbit. Weight 2320 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.
7/5/26. Blood Urea 18 mgms. per 100 c.c.s.
10/5/26. 10 a.m. 1/320th gram Pot.bichrom. in water intraperitoneally.
11/5/26. Urine 10 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- No cells, no casts.
3.15 p.m. 1/320th gram Pot.bichrom. in water intraperitoneally.
12/5/26. Urine 19 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- No cells, no casts.
10.15 a.m. 1/320th gram Pot.bichrom. in water intraperitoneally.
13/5/26. Urine 4 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- One or two epithelial cells, one or two doubtful casts.
14/5/26. Urine 1 c.c. Albumen negative to boiling and nitric acid tests. Micro:- No cells, no casts. (The recent deficiency in the amount of urine was suspected to be at least partially due to the fact that the animal was eating very little; water was put into the cage and the rabbit drank rather greedily).
15/5/26. Urine 14 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- No cells, no casts.
11 a.m. 1/80th gram Pot.bichrom. in water intraperitoneally.
17/5/26. Urine (2days) 16 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- No cells, no casts.
9.45 a.m. 1/80th gram Pot.bichrom. in water intraperitoneally.
18/5/26. Urine 8 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- No cells, no casts.
9.45 a.m. 1/40th gram Pot.bichrom. in water intraperitoneally.
19/5/26. Urine 13 c.c.s. Albumen positive to boiling and nitric acid tests.
Esbach 3 grams per litre. Micro:- Numerous epithelial and hyaline casts.
20/5/26. Urine 9 c.c.s. Albumen positive to boiling and nitric acid tests.
Esbach 2 grams per litre. Micro:- One or two degenerating epithelials: no casts.
10.15 a.m. Blood Urea. 80 mgms. per 100 c.c.s.
21/5/26. Urine 12 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- No cells, one or two hyaline casts.
10.30 a.m. 1/60th gram Pot.bichrom. in water intraperitoneally.

22/5/26. Urine 17 c.c.s. Albumen ? negative to nitric acid test, negative to boiling test.
Micro:- No cells, no casts.
10.15 a.m. 1/40th gram Pot.Bichrom. in water intraperitoneally.
24/5/26. Urine (2 days) Very small quantity. Albumen negative to Nitric acid and boiling tests.
Micro:- Epithelial cells, and some hyaline, and one or two epithelial, casts.
25/5/26. Urine 8 c.c.s. Albumen negative to nitric acid and boiling tests. Micro:- No cells, no casts.
9.45 a.m. 1/40th gram Pot.Bichrom. in water intraperitoneally.
26/5/26. Urine 18 c.c.s. Albumen slightly positive to nitric acid and boiling tests.
Micro:- No cells, no casts.
Died to-day.
P.M.
Right kidney 7.92 grams. Left kidney 8.62 gms.

$$\frac{\text{Kidney}}{\text{Body Wt.}} = \frac{16.54}{2320} = .007.$$

The capsule stripped readily, leaving a smooth surface. The cut surface was congested and oedematous. There was some brownish staining of the portion of cortex next to the medulla.

Spleen.-
Pulp very soft, with an appearance and consistence like red oil paint. The organ is rather small for the size of the animal.

Liver,-
Showed marked patchy yellow areas of necrosis.

Microscopic examination:-

Liver
Extensive patchy necrosis of liver cells. Both the naked eye and the microscopic appearances, and the fact that the animal appeared comparatively well before the last injection, suggest that the last injection was (accidentally) intrahepatic.

Kidneys.
The glomeruli were congested, though some dilated capillary loops were empty. There was no cellular infiltration of the tufts. The endothelial cells were only occasionally swollen, but in some glomeruli most of them showed karyorrhexis. In these tufts, many endothelials had completely disappeared. Occasionally, a portion of a tuft was necrotic. The tuft epithelium was deficient in

very many places. In most places, no remains of it could be seen, at other times a few swollen or karyorrhectic nuclei remained in situ or were desquamating into the capsular spaces. In the majority of the capsular spaces there was albuminous exudate, often forming a crescent on the outer wall but sometimes filling the space, and distending it. The "parietal" capsular epithelium was often imperfect or swollen, and in some places showed distinct though slight proliferation. Occasionally, there was a mosaic appearance in the albuminous material, lying against the outer aspect of the space, suggesting that this appearance might partly be derived from degeneration of proliferated capsular epithelium.

There was no increase of interstitial tissue, and no interstitial oedema, or appreciable cellular infiltration of the interstitium.

The convoluted tubules showed some catarrh. Some cells were vacuolated. Many were swollen, with rather deeply staining cytoplasm and large faint nuclei. This was the typical appearance in most of the convoluted tubules (probably latter part of first and whole of second, together with the broad part of the loop of Henle.)

Other cortical tubules, apparently chiefly early parts of the first convoluted tubules, showed a remarkable degree of pyknosis with faintly staining cytoplasm, and very marked catarrh.

Fat:- Fat was very abundant in practically all the broad parts of the loops of Henle; and there was a much finer dusting at the bases of some of the cells of the convoluted tubules.

A few of the glomerular capsules showed a little fat.

No fat was visible within the glomeruli.

Summary:-

The changes are marked both in glomeruli and tubules, though perhaps a little more marked in the latter. In the glomeruli, the alterations are both endo-glomerular and epiglomerular (-covering epithelium) but the latter changes are rather more severe and more extensive. The capsular spaces and capsular epithelium ("visceral and "parietal") show extensive changes over tufts, the interior of which show only marked congestion and some endothelial swelling; where endothelial karyorrhexis and necrotic changes are present within the

tufts, the changes in the covering epithelium are even more severe.

The picture is consistent with the results of a dosage very high for this rabbit, and particularly of a very high concentration of the poison reaching the kidneys. For a reason we have not been able to understand clearly, the total urine of this animal was always most remarkably low, as will be seen from the protocol, and it is likely that a greatly reduced fluid intake contributed, for there was no oedema at all. This would result in a higher concentration of the chrome reaching and injuring the glomerular endothelium. The capsular epithelium was exposed to the same concentration during filtration, and its rather more differentiated nature caused it to suffer a little more severely. Significantly consistent with this view is the unusually high site of the severest tubular lesions - early part of first convoluted tubule.

In passing, this alteration in site of maximum damage, along with alteration in the concentration of the poison, is much more consistent with the "modern" than with the older view of renal function.

On the modern view such an increased concentration would naturally lead to a lesser degree of reabsorption being necessary before damage could be sustained, and therefore to a change in site of the severest lesions (particularly if some of the poison is fixed in the damaged cells). On the older view, on which

certain cells are specially concerned with the excretion of particular poisons, one would expect a change purely in the intensity, and not at all in the site, of the maximum lesions.

In neither tubules nor glomeruli were there any chronic changes, or even any changes which would necessarily eventually lead to any considerable degree of permanent damage or alteration. The interstitial changes also were inconsiderable.

Microphotograph 3.

Rabbit V.

Healthy rabbit. Weight 600 grams.
Urine before injection (5 examinations), nil abnormal chemically or microscopically.
6/8/26. Fasting Blood Urea. 15 mgms. /100 c.c.
7/8/26. 12.30 p.m. 1/80th gram Pot.Bichrom. in water intraperitoneally.
9/8/26. 12.30 p.m. 1/80th gram Pot.Bichrom. in water intraperitoneally.
10/8/26. Urine 40 c.c.s. Albumen negative to nitric acid and boiling tests. Micro:- Crystals, no cells, no casts.
3.30 p.m. 1/80th gram Pot. Bichrom. in water intraperitoneally.
11/8/26. Urine 20 c.c.s. Albumen doubtful to boiling test: positive to nitric acid test.
Micro:- Crystals, one or two epithelials, no casts.
12.15 p.m. 1/400th gram Pot. Bichrom. in water intraperitoneally.
12/8/26. Urine 20 c.c.s. Albumen doubtful to boiling and positive to nitric acid tests.
Micro:- Crystals, no cells, no casts.
13/8/26. Urine 20 c.c.s. Albumen positive to boiling and nitric acid tests. Micro:- Crystals, two epithelial cells, one hyaline cast.
10.30 a.m. 1/400th gram Pot. Bichrom. in water intraperitoneally.
14/8/26. Urine 12 c.c.s. Albumen very faint trace to boiling and nitric acid tests. Micro:- Crystals, no epithelial cells, or casts: one polymorph.
10 a.m. 1/400th gram Pot. Bichrom. in water intraperitoneally.
16/8/26. Urine (2 days) 150 c.c.s. Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.
4 p.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.
17/8/26. Urine 10 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- Crystals, no cells, no casts.
10 a.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.
18/8/26. Urine not examined.
12.15 p.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.
19/8/26. Urine not examined.
9.15 a.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.
20/8/26. Urine 20 c.c.s. Albumen positive to nitric acid and boiling tests. Micro:- Crystals, no cells, no casts.
10 a.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.

21/8/26. Urine 20 c.c.s. Albumen, trace to boiling and nitric acid tests. Micro:- Crystals, one or two cells, no casts.
10 a.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.

23/8/26. Urine (2 days) 80 c.c.s. Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.
4 p.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.

24/8/26. Urine 40 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- Crystals, no cells, no casts.
2 p.m. 1/200th gram Pot. Bichrom. in water intraperitoneally.

25/8/26. Urine 20 c.c.s. Albumen negative to boiling and nitric acid tests. Micro:- Crystals, no cells, no casts.
11 a.m. 1/80th gram Pot. Bichrom. in water intraperitoneally.

26/8/26. Urine 40 c.c.s. Albumen doubtful trace to boiling and nitric acid tests.
Micro:- Crystals, no casts, just two epithelial cells.
1 p.m. 1/80th gram Pot. Bichrom. in water intraperitoneally.

27/8/26. Urine 40 c.c.s. Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.
4.30 p.m. 1/80th gram Pot. Bichrom. in water intraperitoneally.

28/8/26. Urine 20 c.c.s. Albumen positive to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.
Fasting Blood Urea 43 mgms. /100 c.c.
10 a.m. 1/80th gram Pot. Bichrom. in water intraperitoneally.

30/8/26. Urine (2 days) 35 c.c.s. Albumen negative to boiling test, trace to nitric acid test.
Micro:- Crystals, one epithelial cell, a small number of hyaline and granular casts.
Obviously dying.

31/8/26. No urine found, and rabbit dead and cold this morning.
P.M.
Kidneys oedematous. Right Kidney 3.25 grams. Left Kidney 3.4 grams.

$$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{6.65}{600} = .011.$$

Spleen small. Liver normal.

Microscopic Examination.

Liver and Spleen.

No notable alterations.

Kidneys.

The glomeruli were very small, and therefore apparently overcellular, but there could not be said to be any true overcellularity or any increase of connective tissue between the capillary loops. The loops were still patent, although there was no congestion. Both the parietal and the visceral epithelium of the capsule were flattened and pyknotic. Sometimes the condensed glomerulus had shrunk to leave a very dilated capsular space.

There was neither albumen nor cellular material in these spaces. At many other times the space was completely obliterated, and the capsular epithelium had fused. At some points in such glomeruli there appeared to be a commencing fibroblastic invasion through the fused capsule.

There was no generalised increase of fibrous tissue in the cortex, but there was a distinct increase along the vessels, which were rather thickened, and particularly along the afferent arterioles and around their entrance to the glomeruli.

(There was a suggestion sometimes of very slight increase of connective tissue between atrophic tubules. This may have been due to collapse of tubules and condensation of the intervening tissue.)

There was considerable congestion of the boundary zone and of the intertubular plexus of the cortex.

A great many of the convoluted tubules were greatly dilated. They usually contained hyaline casts, and their lining epithelium was very flat, almost like endothelium. Other tubules, though not dilated, were nevertheless atrophic, and their lining epithelium was cubical and the lumen apparently closed. The nuclei of these cubical cells seemed rather large and were pale.

A few tubules showed a considerable degree of catarrh.

The collecting tubules were normal, but there was albuminous material in the lumen of some.

Summary.

There was present only very slight interstitial change, and that was in relation to the vessels, chiefly to the afferent arterioles.

There were marked chronic tubular changes and slighter chronic glomerular changes.

These last consisted either in a very slight infiltrative spread from the afferent arterioles, or from outside the capsule, subsequent to an obliteration of the space.

Much of the glomerular change may have been atrophic in origin and secondary to alterations in the tubules or in the afferent arterioles.

Microphotograph 4.

Rabbit 9.

Healthy rabbit. Weight 990 grams.
Urine before injection (4 examinations), nil abnormal chemically or microscopically.
12/8/26. 10.30 a.m. 1/60th Pot. Bichrom. in water intraperitoneally.
13/8/26. Urine 15 c.c.s. Albumen doubtful to boiling and nitric acid tests. Micro:- A few epithelial cells, no casts.
10.30 a.m. killed.
P.M.
Kidneys apparently slightly swollen. Nil abnormal in other organs.
Right Kidney 4.20 grams.
Left Kidney 4.31 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{8.51}{990} = .009.$

Microscopic Examination:-

Liver and Spleen:-
Nil abnormal.

Kidneys:-
The glomeruli were practically unaltered. In a few there was some congestion, and perhaps a little swelling of the capsular epithelium (visceral).
There were no interstitial changes, but there was some congestion of the intertubular plexus.
Tubules - These showed very distinct changes, though not so marked as in some other chrome kidneys. The damage was most distinct in the loops of Henle but present in most of the convoluted tubules also save the early part of the first convoluted tubule.
There was a little catarrh here and there, and some necrosis of epithelial cells. Many nuclei showed varying degrees of chromatolysis or pyknosis. Other nuclei were quite normal.
There was some breakdown of the luminal parts of some epithelial cells.

Summary.-
There was, therefore, a pretty marked tubular change, and no appreciable glomerular or interstitial change, confirming the view that the damage produced by small doses is purely tubular, and explainable on the basis of exposure of the tubular cells to a higher concentration of the chrome by reabsorption from the tubules.

Rat 14.

Healthy animal. Weight 117.2 grams.
Urine before injection (4 examinations), albumen negative to nitric acid test on 3 occasions: faint trace on 1. Micro:- No cells, no casts.
23/3/26. 11.45 a.m. 1/20th gram Pot. Bichrom. in water intraperitoneally.
Died within an hour.
(This and the next rat were the first animals injected with the chrome, and the suitable dose was not then known. We were not aware till later that there was a considerable literature on chrome nephritis.)
P.M.
Right Kidney .65 grams. Left Kidney .60 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.25}{117.2} = .011.$

Both kidneys were dark brown and deeply congested as was the Liver.

Microscopic Examination:-

Liver and Spleen:-
No important changes. Pigmentation and endothelial cells were prominent in the latter organ.

Kidneys:-
There was great congestion throughout the organ. Everyone of the glomeruli was deeply congested, but they did not show any further alteration. The epithelium covering them was not notably damaged, although it was very occasionally slightly deficient.
The nuclei of the convoluted tubules and broad part of the loop of Henle were beginning to stain a shade faintly and the cytoplasm, especially the tips of the cells, was beginning to crumble away (but see control rats p. 115).
The changes were widespread but slight. The collecting tubules were unaltered. There was no fat apparent anywhere.

Summary:-
It is doubtful if much chrome passed through the kidneys. The animal probably suffered from shock after an overwhelming dose, and died without regaining a blood pressure sufficiently high to cause any appreciable amount of filtration. The same applies to the next rat.

Rat 15.

Healthy rat. Weight 182.2 grams.
Urine before injection (4 examinations) nil abnormal chemically or microscopically.
23/3/26. 11.45 a.m. 1/10th gram Pot. Bichrom. in water intraperitoneally.
Dead within an hour. (See previous experiment).
P.M.

No obvious lesions save brown staining and deep congestion of the viscera.

Right Kidney .97 grams. Left Kidney .96 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.93}{182.2} = .011.$

Spleen .62 grams.

Microscopic Examination:-

Liver and Spleen:-
Congestion.

Kidneys:-
The observable changes were exceedingly slight, and corresponded to those in rat 14, save that there seemed to be here a rather greater loss of glomerular epithelium.

Discussion of Author's Experiments with Potassium Bichromate.

Potassium Bichromate has, as numerous previous observers have shown, a very marked effect on the kidneys. In fatal cases, it is difficult to tell to what extent the renal lesion determined death in our animals. Certainly no lesions of anything like equivalent severity were found in other organs. The changes in the kidneys were so marked that one cannot conceive that they could exist without there being renal insufficiency. This is corroborated by the invariable rise of blood urea which occurred, and indeed death from uraemia might have been presumed under the circumstances in these animals were it not for the remarkable case of chrome poisoning in man so clearly detailed by Major, and quoted in the historical review under chrome poisoning (P 93). He found that, although the blood urea was very greatly raised, uraemia was not present. However, in our experiments, repeated injections were usually given, and they cannot therefore be regarded as quite comparable.

None of our animals showed any indication of oedema, either during life or at the post-mortem, and in this respect they resemble Major's case. With regard to chlorides, we made no accurately quantitative record, but the daily urine was titrated in the usual manner (Volhard method) and the output per diem was never distinctly lowered until a stage had been reached when the animal was obviously eating very little, or until an oliguria developed which was of itself of a degree sufficient to involve diminished chloride excretion (Major's case showed chloride retention, however).

Sufficient doses had a marked effect in producing a temporary oliguria, but usually this soon passed off, and was succeeded by a normal or increased secretion of urine.

The absence of salt retention - so far as our methods of investigation went, and the absence of oedema may have been related, though not necessarily because salt retention causes oedema. The oedema may of itself produce a salt retention and be due to other factors.

Albuminuria was present in all rabbits except rabbit F, where only very small doses of the poison were given. When present, it was not necessarily produced by the first dose, provided that was small.

Tubular changes were always present, often alone, and where glomerular changes were added, the tubular

were still the more severe.

Where smaller doses were given (rabbits E, V, and 9) there was no endoglomerular change, and only sometimes slight swelling of the capsular epithelium. In these cases, the histological picture clearly indicated that the albuminuria was solely derived from tubular debris. With higher doses (rabbits C,D and F), and particularly where these reached the glomeruli in higher concentration (rabbit F), there was distinct and even very marked endoglomerular alteration. (Microphotograph 3). Even here, however, there was more marked change in the covering epithelium than in the tuft, suggesting that while the two elements of the filter (endothelium and epithelium) are naturally exposed to a similar concentration of the poison, adopting the modern view of renal function, the epithelial cells are rather more sensitive. In no sense was retrogression of tubular changes observed coincidentally with the appearance of acute glomerular changes.

Repeated injections (rabbit D) did not seem to predispose to acute glomerular alterations, nor did any other factor save raising or concentrating the dose reaching the tufts.

The observations were therefore uniformly consistent with the view that with small doses the only elements damaged were the tubules, and that to produce glomerular changes in addition the dose required to be raised very much above that which produced only tubular damage. Rabbit C represents an intermediate change in which predominantly tubular damage is accompanied (Microphotographs 1 & 2.) by a lesser degree of glomerular damage. In these severer cases in which the glomeruli were involved the amount of albuminuria was increased by a contribution from the plasma through the tufts, but the total amount of albumen lost in the course of the experiments was never very high, and probably did not seriously alter the albumen content of the plasma.

In most cases the early part of the first convoluted tubules escaped serious damage, presumably because the poison had not been sufficiently concentrated at that level by reabsorption. All other active portions of the tubule were severely affected (Microphotographs 1 & 2). The one exception to this was rabbit F in which early portions of the first convoluted tubules were the most severely affected parts. This accompanied more sever glomerular

changes than were seen in any other rabbit and oliguria was also present. These facts seemed to indicate an unusual concentration of the poison which would require less or no concentration by reabsorption before attacking the tubules.

In acute cases, interstitial changes were slight and consisted of a patchy round celled infiltration around vessels.

Repeated doses led to alterations in the type of tubular epithelium. Some tubules were completely stripped of their epithelium, others were atrophic and shrunken, whilst others again were greatly dilated, but lined by flattened epithelium. It is an interesting point that atrophic changes in the tubules, even when marked, did not seem to provoke any appreciable increase in the related interstitial tissue. (Microphoto. 4).

In these subacute cases, however, there was a little more marked cellular infiltration round the vessels than in the acute cases, without, however, any degree of alteration which would suggest the poison to be a promising one for the production of any kind of contracted kidney.

Coming to the glomerular changes in subacute cases, they comprised merely a shrinkage and lessened vascularity of the tufts, along with an atrophy of the covering epithelium analogous to that of the epithelium lining the tubules. Where a few fibroblasts were evident in the tufts they seemed to indicate, not the repair of early glomerular damage, but the spread of a slight fibrosis from the afferent vessels. Where some adhesion of the tuft to its capsule had occurred, there was insufficient peri-glomerular change to indicate a local inflammatory origin for this, and the process again seemed to be mainly atrophic.

Lead.

Animals used.-Rats 11 and 12.

No effort was made to study acute lead poisoning.

Rat 11.

Healthy white rat. Weight 175 grams.
Urine before injection (4 examinations), albumen negative to nitric acid tests. Micro:- No cells, no casts, save a single leucocyte on one examination.

11/3/26. 9.30 a.m. 1 c.c. of 1 in 1000 lead nitrate intraperitoneally.

12/3/26. Urine 20 c.c.s. Albumen negative to nitric acid tests. Micro:- No cells, no casts.
4 p.m. 2 c.c.s. of 1 in 1000 lead nitrate intraperitoneally.

13/3/26. Urine 23 c.c.s. Nil abnormal chemically or microscopically.
11.30 a.m. 2 c.c.s. of 1 in 1000 lead nitrate intraperitoneally.

15/3/26. Urine (2 days) 30 c.c.s. nil abnormal chemically or microscopically.
3 p.m. 2 c.c.s. of 1 in 1000 lead nitrate intraperitoneally.

16/3/26. Urine 22 c.c.s. Albumen negative to nitric acid tests. Micro:- Some epithelial cells, no casts.
12.30 p.m. 2 c.c.s. of 1 in 1000 lead nitrate intraperitoneally.

19/3/26. Urine (3 days) 60 c.c.s. Albumen negative to nitric acid tests. Micro:- Nil abnormal.
10.30 a.m. 3 c.c.s. 1 in 1000 lead nitrate intraperitoneally.

20/3/26. Urine 3 c.c.s. Albumen very faint trace to nitric acid test. Micro:- Nil abnormal.
11 a.m. 3 c.c.s. 1 in 1000 lead nitrate intraperit.

22/3/26. Urine(2 days) 22 c.c.s. Albumen negative to nitric acid tests. Micro: Nil abnormal.
4.30 p.m. 3 c.c.s. 1 in 1000 lead nitrate intraperit.

23/3/26. Urine 15 c.c. Nil abnormal chemically or microscopically.
12 a.m. 3 c.c. 1 in 1000 lead nitrate intraperit.

24/3/26. Urine 16 c.c. Albumen negativ e to nitric acid tests. Micro:- A number of renal epithelial cells, one granular cast.
11 a.m. 4 c.c. 1 in 1000 lead nitrate intraperit.

25/3/26. Urine 30 c.c. Albumen negative to nitric acid test. Micro:- A large number of epithelial cells, one epithelial cast.
11 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.

26/3/26. Urine 20 c.c. Albumen negative to nitric acid test. Micro:- A moderate number of epithelial cells, no casts.
11 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
27/3/26. Urine 25 c.c. Nil abnormal chemically or microscopically.
11 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
30/3/26. Found dead, not yet cold, this morning.
(Urine about 2 c.c. Albumen negative to nitric acid test. Micro:- A single epithelial, no casts)
P.M.

Right Kidney 2.02 grams. Left Kidney 1.44 gms.

$\frac{\text{Kidney}}{\text{Body Wt.}} = \frac{3.06}{175} = .017.$

Microscopic Examination.-

Spleen and Liver:-
In the former congestion, in the latter no significant alteration.

Kidneys:-
They were not congested. The glomerular capillaries showed little alteration, but some of the endothelial nuclei showed karyorrhexis and a few here and there had disappeared. Cellular infiltration or fibrosis of the tufts was not found. The epithelium covering the tuft was, however, lost in quite a number of places. The parietal epithelium of the capsule was more altered than the tuft epithelium, showing swelling and, in some cases, desquamation. There was albuminous material in a number of capsular spaces. In most it appeared to be derived by degeneration of the (parietal) capsular epithelium, particularly of the portion adjacent to the point of exit of the tubule. In the rat it was repeatedly noted that the more cubicle epithelium of the tubules continued for a short distance on to the parietal wall of the capsule, and it was from this portion and from the adjacent part of the tubule that most at least of the albuminous material in the capsular spaces was derived.

Round the larger vessels, both veins and arteries, there was a little round celled infiltration, but we could not feel sure that this was due to the injections, although exactly similar appearances were not found in control rats. There was no atheroma or arterial sclerosis of the vessels.

The convoluted tubules of the cortex and the thick part of the loop of Henle were dilated, and the lining cells showed swelling and degeneration and exceedingly widespread catarrh. Many of the tubules

showed merely a basement membrane and no lining cells. Here and there a proliferated epithelium with darker nuclei and a few mitoses was seen.

The tubular changes were quite unassociated with surrounding increase of interstitial tissue or cellular infiltration thereof. The collecting tubules were practically healthy.

Summary:-

Widespread tubular changes without significant interstitial increase or significant glomerular alteration.

Rat 12.

Healthy rat. Weight 140.2 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

11/3/26. 9.30 a.m. 1 c.c. 1 in 1000 lead nitrate intraperit.

12/3/26. Urine 22 c.c. Albumen negative to nitric acid test. Micro:- Nil abnormal.
4 p.m. 2 c.c. 1 in 1000 lead nitrate intraperit.

13/3/26. Urine 26 c.c. Albumen negative ? to nitric acid tests. Micro:- Nil abnormal.
11 a.m. 2 c.c. 1 in 1000 lead nitrate intraperit.

15/3/26. Urine (2 days) 21 c.c. Albumen negative to nitric acid test. Micro:- One or two epithelial cells, no casts.
3 p.m. 2 c.c. 1 in 1000 lead nitrate intraperit.

16/3/26. Urine 10 c.c. Albumen trace ? to nitric acid test. Micro:- No cells, one or two granular casts.
12.30 p.m. 2 c.c. 1 in 1000 lead nitrate intraperit.

19/3/26. Urine (3 days) 28 c.c. Nil abnormal chemically or microscopically.
10.30 a.m. 3 c.c. 1 in 1000 lead nitrate intraperit.

20/3/26. Urine 2 c.c. Nil abnormal chemically or microscopically.
11 a.m. 3 c.c. 1 in 1000 lead nitrate intraperit.

22/3/26. Urine (2 days) 19 c.c. Albumen negative to nitric acid tests. Micro:- A single epithelial cell, one granular cast.
4.30 p.m. 3 c.c. 1 in 1000 lead nitrate intraperit.

23/3/26. Urine 6 c.c. Nil abnormal chemically or microscopically.
11.45 a.m. 3 c.c. 1 in 1000 lead nitrate intraperit.

24/3/26. Urine 22 c.c. Nil abnormal chemically or microscopically.
11 a.m. 4 c.c. 1 in 1000 lead nitrate intraperit.

25/3/26. Urine 27 c.c. Albumen negative to nitric acid test. Micro:- No cells, no casts.
11 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.

26/3/26. Urine 31 c.c. Albumen negative to nitric acid test. Micro:- A few leucocytes and epithelials, no casts.
11 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.

27/3/26. Urine 16 c.c. Nil abnormal chemically and microscopically.
11 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.

29/3/26. Urine (2 days) 26 c.c. Nil abnormal chemically or microscopically.

30/3/26. Urine 4 c.c. Nil abnormal chemically or microscopically.

31/3/26. Urine 15 c.c. Nil abnormal chemically or microscopically.

1/4/26. Urine 20 c.c. Nil abnormal chemically or microscopically.
11 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
2/4/26. Urine 15 c.c. Albumen negative to nitric acid test. Micro:- No cells, a single hyaline cast.
10 a.m. 5 c.c.1 in 1000 lead nitrate intraperit.
3/4/26. Urine 7 c.c. Albumen trace to nitric acid test. Micro:- Some epithelial cells, no casts.
10 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
5/4/26. Urine (2 days) 27 c.c. Nil abnormal chemically or microscopically.
3 p.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
6/4/26. Urine 20 c.c. Nil abnormal chemically or microscopically.
10 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
7/4/26. Urine 12 c.c. Albumen negative to nitric acid test. Micro:- One or two epithelial cells, no casts.
9.45 a.m.5 c.c.1 in 1000 lead nitrate intraperit.
8/4/26. Urine 3 c.c. Nil abnormal chemically or microscopically.
10 a.m. 5 c.c.1 in 1000 lead nitrate intraperit.
9/4/26. Urine 1 c.c. Nil abnormal chemically or microscopically.
10 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
10/4/26. Urine 3 c.c. Albumen negative ? to nitric acid test. Micro:- No cells, no casts.
10 a.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
12/4/26. Urine (2 days) 5 c.c. Albumen faint trace to nitric acid test. Micro:- Nil abnormal.
4 p.m. 5 c.c. 1 in 1000 lead nitrate intraperit.
13/4/26. Urine 17 c.c. Nil abnormal chemically or microscopically.
Found dead this morning.
P.M.

Rat emaciated. The kidneys showed a yellowish brown outer surface of rather mottled colour. On the cut surface the cortical colour was similar whilst the medulla was lighter - brownish pink. The boundary zone was an opaque brownish yellow.

Liver rather pale yellow.

Spleen deeply congested. Malpighian bodies prominent. Weight 1.87 grams.

Right Kidney 1.22 grams. Left Kidney 1.31 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{2.53}{140.2} = .018.$

Microscopic Examination:-

Spleen:-
Congested pulp and prominent Malpighian bodies. Excess of pigment in the pulp and in endothelial cells.

Liver:-
No notable change.

Kidneys:-
The changes corresponded very closely to those in the previous lead injected rat (rat 11). That is, there was very marked and widespread tubular degeneration and atrophy with some attempts at epithelial regeneration. Similar minor changes were present in the epithelium of the capsule and there was the same absence of endo-glomerular alterations.

There were, however, no appreciable round celled accumulations anywhere.

Other minor difference consisted in some pyknosis and catarrh in some of the collecting tubules, and in an occasional slight fibrous thickening of Bowman's capsule, the corresponding parietal epithelium being in such places absent or atrophic.
Microphotograph 5.

Summary:-
The changes induced in these two rats by chronic lead poisoning are almost entirely tubular. Glomerular, interstitial and arterial changes are absent. The perivascular infiltrations are slight, and are found in only one of the rats (the one injected over the shorter period).

Here as with chrome we appear to be dealing with a tubular poison which produces its lesions during concentration of the glomerular filtrate on reabsorption.

The experiments give no support to the opinion that extensive and sustained tubular damage leads of itself to a fibrosis ("replacement" fibrosis).

Hare I

This was the only animal (apart from rats) in the whole series that showed a trace of albuminuria prior to the first injection. It was at first discarded, but later used, during a shortage of animals, for the "acute" experiment now to be described.

The intention was to disregard all changes of standing. The hare was old, probably 6 years old, and had never been injected previously. It had been kept solely for breeding purposes. No other animal in the series was of anything like comparable age.

As the hare died within 24 hours of the injection given, there was little difficulty in separating the recent from the chronic changes.
Weight 3000 grams.

19/6/25. 20/6/25. 22/6/25. Faint trace of albumen to nitric acid test. Doubtful to boiling test.
Micro:- Nil abnormal.

Discarded at that time; used over a year afterwards.

12/7/26.-14/7/26. Urinary findings similar to above.

14/7/26. 10a.m. 8c.c. Sat. Sol. Ferric et Ammon. Citras Intraperitoneally.
15/7/26. Dead but warm this morning.

P.M.

The bladder urine post-mortem contained iron and albumen. There was still some iron in the peritoneal cavity.
Liver:- pigmented.
Spleen:- 2.3 grams. Congested and soft, though the pulp was not diffluent. The Malpighian bodies were not conspicuous.

Kidneys:-

Prussian Blue.(Frozen Sections):- Here and there a tubule-shaped cylinder of iron-reacting material was seen in the cortex, representing apparently a very localised piece of early first convoluted tubule. These cylinders occupied the whole lumen and wall, and no tubular cells were present at these sites. The deepest staining was always at the margin of the cylinder-i.e. corresponded to the bases of the original cells. Similarly, in some places where necrotic remains of cells were still visible, there was often a strong reaction at the bases of these cells.

A very little iron-reacting material was seen in the interstitial tissue here and there in the medulla and in one or two cases lying free in the

lumen of tubules. Nowhere in the cortex was visible iron associated with any but very necrotic "secreting" cells.

Paraffin Sections.

The glomerular tufts were just a little overcellular, due to slight increase of endothelial and round cells. In the whole section there were just one or two tufts showing advanced fibrosis. The capsules often showed a little fibrous thickening. Some glomeruli were unusually near the cortical surface. This surface was slightly uneven, but the depressions were not related to any increase of fibrous tissue.

There were thus slight chronic changes in the glomeruli, and no changes which could be said to be certainly recent and due to the injection.

The interstitial tissue showed patchy cellular increase in the boundary zone. There was also slight round celled infiltration and increase of connective tissue around the afferent arterioles and larger vessels.

There were no focal scars in the cortex, and there was no general increase of interstitial tissue. There were no recent alterations save a little occasional iron pigment.

The tubules showed no evidence of chronic changes. Recent changes were, however, marked. There was a great deal of catarrh throughout the convoluted tubules, with pyknosis and other degenerative changes in the nuclei; there was iron pigment in degenerating cells here and there. The changes were similar in the loops of Henle.

No fat could be detected in the organ.

Summary:-

A fulminant tubular nephritis, with practically complete lack of glomerular change.

Conclusions regarding Chemical Nephritis in general.

We have dealt briefly with the literature on thirteen of the chemical substances most commonly used in the experimental production of nephritis, and have recorded personal experiments with three of these. Other substances e.g. arsenic, have been used, but these poisons dealt with have been more adequately studied. There is little doubt that the list of such substances may be indefinitely increased in the future. But is this going to be much importance? It seems that all these poisons have a distinctly uniform type of effect on the kidney. They are at least as true to type as the nephritis of man, and in certain respects they are perfectly distinct from ordinary human nephritis.

The differences between individual poisons are not nearly so striking as the resemblances.

The calcification in mercuric chloride poisoning, and the hyaline droplets in the glomerular endothelium in uranium poisoning, are certainly typical of these particular poisons, though not actually confined to them; but, the special action of individual poisons scarcely affects the uniformity of the results, and does not modify the essential character of the lesions - namely, their tubular distribution.

When, as happens occasionally, with chrome or mercury etc., we get a human case of such poisonings, it proves true to type, and produces in man a chemical nephritis, unlike ordinary nephritis but similar to the experimental results with the same substance.

Later we shall find occasion to believe that chemical nephritis, with its initially purely tubular incidence, stands quite by itself and differs both from human nephritis and from bacterio-toxic experimental nephritis.

A further feature of chemical nephritis is that while the damage is always of purely tubular type if the minimum kidney-damaging dose be used, and the dose has as a rule to be raised very considerably above this minimum before any appreciable glomerular damage is caused.

This is true even of chemical poisons which have been repeatedly classified as "glomerular" (cantharidin, uranium, chrome). We do not believe that a predominantly glomerular poison of simple chemical nature has been proved to exist.

With dosages near the minimal does referred to, any glomerular alterations are practically confined to the covering epithelium, which may be a little swollen. (Examples of dosage producing such almost purely tubular changes are found in at least two of our chrome rabbits - 9 and E). When, however, the dosage and especially the blood concentration of the poison is raised beyond a certain limit, endoglomerular changes become manifest (nuclear karyorrhexis, necrosis etc.) and with further increase of dosage these become more and more marked. The tubular alterations, and the alterations in the capsular epithelium at least keep pace with these added endoglomerular changes, and remain the more severe. Rabbit C shows (Microphotograph 2) a slighter degree of this superadded glomerular change. Rabbit F a greater degree. (Microphotograph 3).

This sequence is almost perfectly explained on the modern theory of renal function. The tubular changes are produced, not because their epithelium is necessarily more susceptible than the endothelium of the glomeruli but because the dilute poison may be in only practically harmless concentration in the glomerular capillaries. After filtering through the tuft into the capsular space it retains an identical concentration. Any slight changes that occur in the capsular epithelium ("visceral" or "parietal") are due merely to a greater sensitiveness of these cells, but after all such changes are not invariable. As the filtrate passes down the tubules, however, it is gradually being concentrated by reabsorption of flued from it, and at some point or other, varying with the initial concentration, it becomes decidely more toxic to the lining cells, and lesions are produced. A vast amount of disagreement in the literature as to the precise site of these tubular lesions will be cleared up if we admit that there is no necessarily constant site of the tubular damage caused by any one poison, but that the site of maximum damage is the site at which, with the particular dosage and method of injection employed a suitable concentration has been reached.

It is significant that the poisons for which a localisation of the lesion in the first convoluted tubules has most frequently been claimed (chromium:cantharides) are precisely those in which glomerular lesions are most easily produced, and indeed have sometimes been claimed as the chief lesions. In other words, these are precisely the poisons in which the dose has been in highly toxic concentration in the blood. On the other hand, when less toxic substances have been used, substances of which high dosage had to be given to produce any affected at all, (e.g. uric acid), the lesions have been low in the tubules. Similarly, intravenous adminstration, has tended to give lesions higher in the tubules than other methods of adminstration, for here again the blood concentration of the poison is higher (e.g. Shaw Dunn: oxalate nephritis). In our own experiments with chrome, we have observed (Rabbit 7) that similar variations in the site of the lesion depended on the initial concentration of the poison.

This varying site of tubular incidence whilst natural on the "modern" view is almost inexplicable on the "secretory" theory.

With regard to the lesser degree of changes sometimes observed still lower down in the tubules, these are explained if we regard the damaged cells as having combined with some of the poison and so reduced its concentration. Further, if the lesion was not produced till the concentration was at its maximun, i.e. till equilibrium had been reached, the contact of the toxic molecules in the filtrate with the inner cell membrane would be less intimate, for, higher up, the continious withdrawal of fluid must constantly "strand" many of the rejected poison molecules on the inner cell surfaces, and tend to a special concentration just at that point.

If this argument be correct, it follows that it is unlikely that any other simple crystalloid chemicals used to produce chemical nephritis, will produce significantly different general results. Even supposing a particular chemical poison to have, as might well be, quite a considerable selective action on endothelium and therefore on the glomeruli,

this would be more than balances by the greater concentration of the poison in the tubules. The concentration resulting in the tubules has been worked out by the Cushny (33). In an actual experiment he found the filtrate in a cat to be concentrated 120 times (12 litres of filtrate gave ·1 litre of urine). This may seem an extraordinarily large figure but reference to Cushny's argument will show that it requires only the filtration of a quite minute quantity of filtrate per glomerulus per unit of time. Taking this figure it is evident that before the minimal kidney-damaging dose would produce glomerular rather than tubular changes, the endothelium would have to be over 120 times more sensitive to the poison than the tubular epethelium - an exceedingly unlikely thing. Further it is evident that if, as we hold, noncrystalloid toxins are not filtered initially by the glomeruli, we may expect their actions to be radically different.

Subacute and Chronic Chemical Nephritis.

We turn now to the attempted production of subacute and chronic lesions by the use of these poisons. Here we are on rather difficult ground, but we believe that, when due allowance is made for spontaneous nephritis there is no evidence that any chemical poison can produce more than an insignificant degree of progressive interstitial or glomerular change. With very few exceptions, the experimenters who claim to have produced a chronic interstitial nephritis, describe in detail a non-glomerular focal interstitio-tubular change - i.e. spontaneous nephritis. The renal localisation of this 'spontaneous' infection may have been provoked by the poisons injected, but this does not render the late lessions a direct sequel of the acute ones.

Chemical nephritis as an example of pure Tubular Nephritis.

It is probable that these various nephritides now being considered present a tubular nephritis in a purer form than do any identifiable group of cases in man.

What are the signs and symptons of

tubular nephritis as indicated by these animals?

The blood urea is raised. Probably (Browne , P.103) it is raised for only a short period and tends to fall between injections. Albuminuria is constant but slight, and the urine shows many epithelial cells and casts.

There may be a passing phase of oliguria but polyuria is more typical. Oedema is often absent (present in uranium poisoning, absent in chrome poisoning). Salt retention is inconstant. It is doubtful, in spite of the high blood urea, if uraemia is present.

The raising of the blood urea is probably, as was first suggested by Shaw Dunn, due to the fact that the damaged tubular cells, in reabsorbing fluid from the filtrate, fail to exclude urea from this reabsorbed fluid. It may be that this particular function fails before the cells are sufficiently damaged to allow of a similar reabsorption of creatinin and other lower threshold bodies. Their antagonism to the passage of these bodies must be a more tenacious one even normally, than their antagonism to urea, for even normally they are much more nearly completely excluded from the reabsorbed fluid than is urea (Cushny . 33.). Possibly substances associated with uraemia production are amongst the very low threshold bodies, and this might explain an absence of uraemia. Our knowledge of the causes of uraemia is not, however, sufficient to enable us to pursue this point further.

Albuninuria and Casts.

In the slighter degrees, in purely tubular cases, therefore, we would expect only a relatively slight albuminuria, derived from extensive disintegration of epithelial cells. Epithelial cells, and casts showing evidence of origin from epithelial debris, would, we might expect, be prominent in the urine. This is exactly what we do find.

Moreover, when, as in our lead experiments, repeated dosages each below the glomerulus-damaging level, are given the albuminuria becomes very slight and intermittent, and is merely the expression of a slower tubular catarrh. This was confirmed by the fact that the usual urinary abnormality in these rats was the finding of a few epithelial cells without casts.

In heavier poisonings, there is a more marked albuminuria, contributed to by the plasma because the glomeruli are now injured. The glomerulus-damaging dose is, however, not usually far from a fatal one, and it is rarely possible therefore to sustain a copious albuminuria over any length of time, or to produce any considerable alteration in the albuminous content of the plasma.

Oedema.

There are several possible explanations of the lack of oedema in some instances. It is true that in some chemical nephritides investigated chloride retention has been slight whereas urea retention was considerable. (Underhill. Tartrate nephritis p. 104 and our own chrome experiments p. 135).

This fits in with the view that would relate oedema to salt retention. But the relationship is not invariable. In Major's case of chrome nephritis in man there was marked chloride retention but no oedema.

An alternative explanation suggests that oedema may usually be due to a loss of albuminous material from the plasma, thus lowering its osmotic pressure. This would lead to a diminished capacity on the part of capillary vessels generally to absorb fluid from the tissues. The tendency is accentuated because it is the smaller albumen* molecule that naturally passes more readily through the damaged glomerular filter, and of course it is the smaller molecules that are most efficient in sustaining osmotic pressure. Such a mechanism has been described by Ruszńyak (149) amongst others. Now, even where "tubular" chemical poisons are given in doses which also damage the glomeruli, the total loss of albuminous material from the plasma is not high, and the consequent oedema producing action cannot be great. However, as oedema does occur with some chemical poisons (e.g. uranium) this is not by itself a satisfactory explanation. Especially is this the case since some (Linder, Lundegaard, and Van Slyke 190) while admitting a relation of

* As against the globulin.

plasma-albumen loss to oedema, point out that quite a considerable loss may occur before there is any oedema producing effect.

There is yet another possible factor, and it seems more likely to be at work here than either of the others. Chrome has little selective action on endothelium, and consequently the undamaged capillaries of the general circulation do not allow of an abnormal transudation of fluid into the tissues. Uranium does specially damage endothelium, as is indicated by the hyaline droplets in the endothelial cells of the glomerulus. There is no reason to believe that the endothelium of the glomerular capillaries is especially sensitive to the poison and a similar damage to capillaries throughout the body may explain the oedema of uranium nephritis. This view of the causation of oedema is expressed by Underhill (162). He refers also to views previously put forward by himself with Bogert and Mendel, in which they hold that nephritis produces a change in the permeability of the walls of the capillaries of the general circulation.

Oliguria and Polyuria.

The transient oliguria is usually present only after a pretty large dose, and probably indicates a passing glomerular stasis, with temporary suspension of filtering function. The more typical polyuria is explained by the inability of the damaged tubular cells to concentrate the filtrate properly.

Nephritis Changes produced experimentally by Substances of Bacterial origin and related Toxins such as Ricin and Abrin.

Having, we believe, obtained the anticipated uniformity in fundamental type for chemical poisons. we seek to test the validity of our other hypothesis - that the present group will also show a type change, and a different one from the previous. This, as will be remembered, was a suggestion based on the colloidal nature and non-filterability of toxins.

Literature.

We have now to review the literature of experimental nephritis produced by bacteria, their toxins and allied substances. We shall record and summarise the findings with different substances one by one, but shall delay interpretation of the changes till all are recorded, and our own experiments noted.

Snake Venom.

Snake venom has been used by a number of observers.

Novak (111) found that it produced necrotic changes in the epithelium of the renal tubules.

Pearce (128) in a series of 21 rabbits to which he gave single doses of snake venom found two characteristic changes - haemorrhages into the tufts but not into the capsular spaces, and exudation of R.B.C. serum and fibrin within the tufts, with or without haemorrhages. Few polymorphs were seen. The tubular epithelium and the cells lining Bowman's capsule were uninjured. He regarded the action therefore as apparently selective on the glomerular endothelium, dissolving it.

With repeated doses, he found that there was proliferation of the tuft epithelium, but only where haemorrhages had occurred. Tubular degeneration became extensive in later stages, In the animals which survived longest, little glomerular change was found.

In dogs, he produced hyaline changes in the glomerular capillaries, together with tubular degeneration. He concluded that the changes induced by the venom did not tend to become chronic (130).

Suzuki (159) found glomerular changes to predominate. Indeed, in the acute stage there was little tubular change. The changes were similar to those described by Pearce - endoglomerular, with less change in the epithelium of the tuft. Large cystic spaces containing blood and fibrin were found within the tufts, and these were followed after a week by marked endothelial proliferation, and a little later by degenerative changes in the arteries of the organ, and tubular atrophy. Still later, there was an increase of interstitial tissue, especially around Bowman's capsule. He considered the interstitial changes and tubular atrophy to be secondary to the glomerular lesions. Neither parietal nor visceral epithelium of the capsule showed much change at any stage.

In further experiments, using rabbits, he claimed that he was able to produce granular contracted kidneys by allowing the animals to live for many months after a single large dose or one or more moderate doses. The left kidney was in some cases early removed as a control. Leiter (88), however, regards these contracted kidneys as results of spontaneous nephritis. Certainly, a single dose of toxin does not seem likely to produce a <u>focal chronic</u> nephritis such as Suzuki describes.

Summary.

The effects of snake venom seem to follow a definite sequence - endoglomerular changes are the earliest. Only later are epiglomerular and tubular lesions produced. It is doubtful if interstitial or progressive glomerular lesions have been produced at all.

Serum of Eels.

Petit (132) claimed to have produced a predominantly tubular lesion with the serum of eels, but the substance has not been sufficiently studied to give any definite conclusions.

Ricin and Abrin.

Employing this substance, Flexner (50) obtained accumulation of leucocytes in certain capillaries, sometimes with imperfect thrombus formation. Fibrin was observed occasionally in the larger vessels, and in the glomerular capillaries. The tubules were also degenerated, but the epithelium of the capsule, parietal and visceral, suffered severely.

Changes are thus described within the tufts, in their covering epithelium, and in the tubules. It is difficult from the description to estimate their relative prominence, but the changes in the glomerular epithelium are definitely stated to be greater than those in the tubules.

Diphtheria Toxin.

When considering the experimental results obtained with such a substance as diphtheria toxin, it has been thought advisable to include in the review investigations of the kidneys of fatal cases of diphtheria in man.

Human Cases.

Ortel (113) found that in the majority of his cases with diphtheria, the organism was not present in the kidneys, yet the glomeruli showed proliferation of their endothelium, along with degeneration and desquamation of the epithelium, both parietal and visceral, of Bowman's capsule.

Degenerating polymorphs were observed in the tufts, and occasionally albumen in the capsular spaces. There were focal round celled accumulations round the

glomeruli, between the tubules, and in relation to larger vessels; and haemorrhages in the interstitial tissue and into the tubules. The secreting tubules showed marked changes.

Langhans (86) found granular degeneration in the cells of the convoluted tubules, and especially in the broad part of the ascending limb of the loop of Henle. The glomeruli showed slight swelling of the capillary endothelium. The interstitial tissue showed but slight changes.

Cornil and Brault (29) found the tubules to be specially affected; the glomeruli and interstitial tissue showing little beyond congestion.

Bernhardt and Felsenthal (10) found hyaline changes in the capillaries of the glomeruli and proliferation of their endothelium, together with degeneration of the epithelium of Bowman's capsule, parietal and visceral. In only a few cases did they find focal accumulation of round cells around Bowman's capsule.

Rosenstein (144) found no marked or constant changes. Any that were observed were usually slight degenerative changes in the convoluted tubules.

Councilman, Mallory and Pearce (31) found acute glomerular nephritis with proliferation of the capillary endothelium and hyaline thrombi. Proliferation and desquamation of the epithelium of Bowman's capsule, parietal and visceral, and haemorrhagic or fibrinous exudation into the capsular space were also observed on occasion. The secreting tubules showed necrotic or degenerative changes. In 24 out of 103 cases, however, the chief lesion was an interstitial nephritis with focal or diffuse accumulation of large round cells in the cortex and medulla. In such cases there were degenerative tubular changes but very little glomerular change.

Summary.

These observers obviously differ widely from one another. The difference may turn out to be related to a difference in the time at which the kidneys were examined. If that be so, animal experiments ought to provide clearer results.

Animal Experiments.

Welch and Flexner (171) used both living cultures of the bacillus, and diphtheria toxin. They found the effects of the two indistinguishable. Both tended to produce hyaline swelling of the glomerular capillaries and smaller arteries, sometimes along with fatty changes in the cells of the tubules. Later, Flexner (50) described necrosis of the endothelial cells of the glomerular tufts with karyorrhexis. Sometimes mitotic figures were present. There was degeneration of the epithelium of Bowman's capsule. There was sometimes concurrent tubular degeneration, but this was most marked when there was hyaline degeneration of the vessel walls. No interstitial changes were produced.

Lyon (95) found numerous hyaline thrombi in the glomerular capillaries with only slight swelling of the capillary basement membrane. Some of the endothelial nuclei had disappeared. There was an increase of polymorphs in the tuft, many of them with fragmenting nuclei. In the earlier stages, there was no apparent increase in the total number of nuclei in the tuft, but the epithelium covering it was swollen, and, on the exposed surfaces, mostly desquamated. A few tufts showed rupture of capillaries into one another. A minority of the capsular spaces contained a little albuminous material, near the point of exit of the tubule, and derived, he thought, mostly from the tubular epithelium.

In subacute cases, there was less glomerular congestion, but there was hyaline thickening of the walls of the capillaries and afferent arterioles, which were, however, usually dilated. Albuminous material, apparently derived from the blood, separated individual loops of the tufts. The endothelial nuclei were swollen and, in some cases, cast off into the lumen, helping to block the capillary. The epithelium covering the tuft was greatly swollen, and its cytoplasm was more abundant than usual and sometimes hyaline. In later stages, (beyond the fifth day) cysts, lined by endothelium and containing blood and fibrinous material might be found in some tufts. Fibrous changes were not produced.

Tubular lesions were present in both acute and subacute cases, but were less marked in the latter, and more strictly confined to the ascending limb of the loop of Henle. Casts were found and considered to be of two types (a) albuminous transudate through the tubules (b) from consolidation of cellular debris from the tubular epithelium. From Lyon's description, the

origin of one set from the plasma, of the other from the tubular cells, can scarcely be doubted; but it might be added that the description and site of the plasma-derived casts does not seem entirely to negative an origin by transudation from the glomeruli. The mere fact of the absence of albuminous material from the capsular spaces does not dispose of this possibility, for the albumen might be in very much more dilute form in that site than lower down. Also, the sites in which such casts were noted (chiefly collecting tubules, and to a lesser extent the loops of Henle) are the sites where they would become more demonstrable either by the ordinary process of concentration by reabsorption, or, in the case of the loop of Henle, by a mechanical factor, - the hair-pin bend,- tending to retard the flow of the coagulating albuminous part of the filtrate. The theory of transudation through damaged tubules does not provide a simpler explanation of the localisation, for much the commonest site was the collecting tubules, which were undamaged. Lyon described lesions of both glomerular endothelium and covering epithelium. so that the necessary requirement for albumen leakage through the tufts appear to have been fulfilled.

The vessels were all congested, and around some vessels in the medulla there was round celled infiltration in the subacute cases. Lyon regarded these cells as derived from the blood.

He failed to produce progressive glomerular or interstitial changes.

Bailey (7) found arterio-sclerotic changes in all large vessels of rabbits injected with diphtheria toxin. The endothelium of the glomeruli showed swelling and desquamation with fibrinous thrombi and hyaline masses in necrotic capillaries, and haemorrhages in some tufts. Some glomeruli contained collections of polymorphs. He considered the changes to resemble closely those in acute or subacute nephritis in man. The lack of progressive changes in the glomeruli seems inconsistent with subacute glomerulo-nephritis, and the nephritic process in man seems to have been simulated only in comparatively acute phases.

Faber (47) found the primary change to be proliferation of the endothelium of the tuft. With Larger doses, however, there were also degenerative changes in the endothelium, with rupture of capillaries and production of "blood-cysts" like those described by Lyon. Thrombosis was sometimes noted in capillaries of the tuft. Fibrin, blood cells, and leucocytes were, as Lyon noted, practically absent from the capsular spaces.

Any tubular changes that were found were slight and were regarded as secondary to the glomerular.

Frotheringham (52) by repeated sub-lethal doses failed to produce significant changes in the kidneys. He did not consider the selective action of diphtheria toxin on capillary endothelium sufficiently great to render hopeful the production by it of permanent glomerular lesions.

Leiter (88) described changes similar to those produced by other observers, but emphasised the difficulty of correlating the degree of change with the dosage used. Animals receiving small doses sometimes showed much more severe alterations than those receiving a larger dose. There was extreme hyperaemia and dilatation of the glomerular capillaries, endothelial degeneration, and hyaline thrombosis in some of the loops. In a certain percentage of cases"blood-cysts" were conspicuous. There was a variable amount of precipity ab in the capsular space with only occasionally red blood cells. Tubular degeneration was marked and casts were numerous.

The lack of leucocytic reaction in the kidneys was emphasised. No chronic changes were produced.

Jes Jessen (67) produced only glomerular changes in acute experiments. In rather more prolonged experiments glomerular and tubular changes were found, but still later the changes were entirely tubular. He did not attribute the varying results to the different durations of his experiments but to variations in the method of injection. We consider, however, that probably the explanation lies chiefly in the duration of the experiments.

Summary.

The literature with regard to diphtheria toxin is thus not unanimous, but the general trend is to emphasise the glomerular lesions, and particularly the endoglomerular lesions. Some describe these alone, others, probably with greater dosage, or death at a later stage, describe additional tubular changes. A feature we shall emphasise in our own experiments is

noted by more than one observer - namely, marked endothelial alterations in the glomeruli with albuminous exudate or haemorrhage, which is, however, sub-epithelial in site and has not escaped into the capsular spaces. This is important as giving us a convincing proof of the relatively normal state of the glomerular epithelium at a time when the endothelium is distinctly damaged.

Bacteria etc.

Amongst the earlier workers on experimental nephritis with bacteria were Pernici and Scagliosi (131) who injected dogs with anthrax bacilli, staphylococcus pyogenes aureus, bacillus pyocyameus, and micrococcus prodigiosus. They found in them a glomerulo-nephritis. In only one animal did they claim to have produced a proliferation of the capsular epithelium. They noted haemorrhages and desquamation in the tubules, and in Bowman's capsule, as well as endoglomerular changes. They produced similar but less intense lesions with filtrates of cultures of anthrax bacilli and bacillus pyocyaneus.

Lyon (95) injected into rabbits toluol-killed cultures of staphylococcus aureus from cases of acute osteomyelitis, and obtained some degenerative changes in the tubules, but this was all save for a very slight increase in the cellularity of the interstitial tissue in one of six rabbits.

Klotz (78) injected rabbits with streptococcus viridans obtained from cases of endocarditis. He described acute changes which were mainly glomerular, and chronic changes which he called "chronic interstitial nephritis". His chronic interstitial nephritis is not the same as the disease of man which goes under that name.

He described focal areas of cellular interstitial increase, and, within these, greatly altered tubules and relatively normal glomeruli. The appearances fit in exceedingly well with the description of spontaneous nephritis.

Lecount and Jackson (87) made a contribution whose value has already been commented on in dealing with spontaneous nephritis.

They gave 58 rabbits single injections of living organisms - haemolytic streptococci from septic throats in the great majority of cases. Acute lesions were not invariable, but, when present, consisted of bacterial emboli in the glomerular capillaries and areas of necrosis in the medulla. In only one animal of the whole series did they get more marked glomerular changes - marked disorganisation of the tufts, with disorganisation and haemorrhages within them, and red blood corpuscles in some of the capsular spaces. Most of the animals, however, did not die in acute stages. Many survived for some time, and in some of these changes described as "subacute" were recorded - exudation of lymphocytes and plasma cells around the veins. Yet others, living longer, showed "chronic" changes, - focal interstitial increase, with dilated tubules and retention cysts in relation to these increases. In some places there were apparently regenerative tubular changes. No subacute or chronic glomerular changes were recorded, and the appearances do not seem decidedly different from the type of change the same authors described as spontaneous, or from spontaneous changes we have ourselves found (Microphotographs // 9 12.).

Dick and Dick (37), in an article already referred to (p. 58) described experiments in which they injected into rabbits organisms they had isolated from the urine of human cases of nephritis. With gram negative anaerobic bacilli they got no more than cloudy swelling of the tubules. These are amongst the bacilli whose alleged etiological relationship to nephritis we have previously doubted. In another animal in which gram positive anaerobic bacilli and cocci were used there was fatty degeneration of cells in the glomeruli and convoluted tubules. with some new formation of connective tissue, especially under the capsule (probably spontaneous nephritis J.G.). Bowman's capsule and the tubules contained granular debris. With streptococci, they got degeneration and desquamation of the epithelium of the convoluted tubules and of Bowman's capsule. In short, therefore, they got acute changes in both tubules and glomeruli in some of their cases, but in others got no appreciable

changes. In only one did they get chronic changes, and these were of very doubtful type.

Stoddart and Woods (157) used toxins from cultures of streptococci and staphylococci and Vaughan's split protein poisons. Repeated injections of such substances into rabbits produced no notable glomerular changes.

Coulter and Pappenheimer (30) injected haemolytic streptococci directly into the rabbit's renal artery, and succeeded in producing acute changes only, the organisms disappearing rapidly through the action of polymorphs, which were in a few hours seen in many of the glomeruli. Later on, suppurative foci appeared. Pneumococci were also used, with similar results. Acute glomerular changes were also produced within 24 hours by an extract of dead typhoid bacilli into the renal arteries of sensitised rabbits. As in the other cases chronic changes did not follow.

Faber and Murray (48) also used rabbits and failed to produce chronic glomerulo-nephritis with various organisms - streptococcus haemolyticus, streptococcus viridans, bacillus coli, staphylococcus.

Winternitz and Quinby (172) endeavoured to produce changes by the use in dogs of an organism known to be pathogenic to them especially. Cultures of b. bronchoseptus were injected directly into the renal artery. Acute glomerular and interstitial changes resulted, with albuminuria and haematuria.

Ophüls (119) gives a good review of the literature and claims to have produced a sequence of changes from acute through subacute to chronic by the injection of organisms. Streptococci he regarded as the organisms best adapted to cause the sequence of changes, but other organisms could, he thought, act similarly. He believed that the basis of the whole sequence of progressive changes in human nephritis was glomerular. He considered that the first essential requirement was the production of acute glomerular damage (acute glomerulo-nephritis). From the permanent residual damage of such an attack the whole picture of chronic glomerulo-nephritis was gradually built up. He thought that, while acute and chronic changes might be induced by bacterial toxins, the more likely mode of production, and the most hopeful experimentally, was the use of the organisms themselves, dead or alive. He thought that these formed bacterial emboli in the glomeruli and were lysed there, the damage

being produced by endotoxins released locally by this lysis.

Major (101) used bacillus mucosus capsulatus in rabbits. He described an "acute haemorrhagic nephritis" after single injections. Red blood corpuscles were present in the tufts, between the capillaries, in the capsular spaces, tubules and interstitial tissue. Hyaline fibrin thrombi were present in the glomerular capillaries. After repeated injections especially, he produced marked tubular necrosis, with granular and hyaline casts. In later cases, some of the glomeruli were fibrotic or destroyed, and the kidneys were pitted under the capsule by numerous areas of round celled infiltration, with dilatation of the tubules and desquamation of their epithelium. He also described fibroses around the glomeruli, and the early stages of crescent formation. These are not quite the typical changes of spontaneous nephritis, but we doubt if they are a direct sequel of the earlier lesions described.

Faber (47), continuing his work reviewed already under diphtheria toxin (p.158) tried the effect of using diphtheria toxin followed by injections of b. coli communis. He produced a glomerulo-nephritis in which the changes were at first endoglomerular. Later, these changes were followed by epiglomerular ones, with formation of crescents, etc. (described by him as subacute glomerulo-nephritis).

Subsequently, he failed to reproduce this picture by repeated injections of various organisms without the preliminary dose of diphtheria toxin, which he therefore considered necessary to cause some initial degree of damage to the glomerular endothelium.

Bloomfield (") injected dead streptococci,- haemolyticus and viridans,- directly into the renal artery of rabbits, closely examining the kidney at operation for evidence of spontaneous nephritis. About two weeks later he began a series of intravenous injections of living organisms - from 1 to 19 injections over periods up to 19 months. In 12 of the 16 animals, the kidneys at the end of the experiments appeared to be exactly as before the series of injections was begun. In the other 4, such changes as were found he regarded as spontaneous. Comparison of his descriptions with others in the literature leads one to believe that others of the authors we have been considering would have been less careful and would have described some of the results as positive.

Kuczynski (85) injected mice repeatedly with streptococci and obtained glomerular changes with degeneration followed by proliferation and hyalinisation of the tufts. Leiter (88), commenting on these observations, remarks that hyalinised glomeruli are not uncommon in ordinary mice.

Cary (20) used organisms isolated from nephritics or from septic foci to inject into rabbits and white rats. No positive results were obtained with the rats. The organisms used in the rabbits were streptococcus viridans, feebly gram positive bacilli, staphylococcus aureus, diphtheroids and b.coli. The results were not striking. Usually. if several doses were given, there was some destruction of the tubular epithelium and slight interstitial infiltration with perivascular fibrosis. No contracted kidneys were obtained. He noted that after the first injection the organisms were easily recovered and cultivated from the urine, but that this was difficult or impossible after subsequent injections.

Leiter (88) performed a large series of experiments with streptococcus viridans in rabbits. He varied his procedure considerably, sometimes giving preliminary doses of diphtheria toxin or snake venom, sometimes not. Sometimes the injections were intravenous, sometimes intracardial and in other cases subcutaneous. With none of these methods did he obtain acute, subacute or chronic glomerulo-nephritis. Frequently spontaneous nephritis in varying degrees was found, and its frequency was such as to suggest that the injections favoured its development. The lesions were not, however, analogous to those of nephritis in man.

Clausen (24) dealt ably with an admittedly particular form of nephritis,- focal embolic glomerulo-nephritis such as is produced pre-eminently in cases of endocarditis. This focal embolic glomerulo-nephritis had, as noted in Section 1, been described in man by quite a number of writers (Löhlein, 92 Baehr, 6 Warwick 167) and is well recognised.

It differs chiefly from ordinary glomerular nephritis in that most glomeruli are unaffected, and to reproduce the picture in rabbits Clausen used a heavy growth of streptococcus viridans on plain agar (from a patient with acute "rheumatic" endocarditis). The agar was ground in a mortar with salt solution till a fine suspension was formed, and the coarser particles were then thrown out by centrifugalising. This suspension, or in some cases agglutinated streptococci

without agar, was injected intracardially. The changes in the kidneys were more marked with the larger agar particles than when the agglutinated cocci were used. With agar suspension there were infarcts in nearly half the cases. In all cases, there were agar emboli in some afferent arterioles and tufts. There was exudation of polymorphs replacing some of the tuft endothelial cells in 10 of the 14 cases. In 6 cases there was proliferation of the endothelium of the tufts; in 5 cases crescents were present (the earliest after 6 days). Hyalinisation of some tufts was present in 5 cases (the earliest after 4 days). Atrophy of tubules was first noted after 25 days, and was observed in 3 of the cases.

The percentage of glomeruli involved varied from 4% to 45%, the highest percentage (45%) being produced in an animal which lived 36 days, and received 5 injections.

The results were similar, though less marked, with the agglutinated cocci.

The claim to have produced a focal embolic glomerulo-nephritis similar to that in endocarditis in man seems then to be based on good grounds.

These results may be compared with those of Leiter (88) in the cases in which he injected lycopodium spores with streptococcus viridans directly into the left renal artery. He obtained infarcts and interstitial increase, but less glomerular change, and showed that he could get identical results by using the spores alone. He admitted, however, that the spores were large enough to block the afferent arterioles and did not penetrate into the tufts. It is reasonable from his results to wonder whether Clausen might not have produced the same lesions as he did with streptococcus-agar emulsion with fine emulsions of sterile agar alone. This does not minimise the resemblance of the changes to those in human endocarditis. It merely emphasises the importance of the mechanical part of the action of the emboli in that condition.

Somewhat similar alterations were noted by Gaskell (53) in the kidneys of 3 out of 6 rabbits in which ulcerative endocarditis had been produced experimentally. Infarcts and focal glomerular changes were found. Sometimes the glomerular changes were confined to individual loops of a tuft. The endocarditis had in most cases been produced by streptococci from the normal mouth.

The last experimenters to whom we shall refer here are Duval and Hubbard (42). In 1926, these observers recorded results with scarletinal streptococci and their toxins, along lines of work somewhat similar to those we were at that time following. In their hands, scarlet fever streptococcus endotoxin produced an acute glomerulo-nephritis, although the exotoxin did not. As will be seen, we believe we have obtained positive results with the exotoxin. Sometimes they injected the endotoxin itself, at others they gave large doses of the streptococci to a partially immunised animal, so that lysis of the bacteria produced the endotoxin. The changes described varied from active hyperaemia of the glomerular capillaries, through proliferation of the glomerular endothelium and epithelium, to complete necrosis of the tufts. From an early stage, serum was evident in the capsular spaces and rupture of distended tufts occurred. There was no polymorph infiltration.

In some cases there was proliferation of the capsular epithelium. Save for this last change, the picture in our exotoxin rabbits was very similar. The crescents they described always began in the "tubular" portion of the capsule, and blocked the exit - sometimes while the tufts seemed otherwise still capable of function.

The conclude their paper with a photograph, microphotograph and description of an immunised rabbit's kidneys. This rabbit had been subjected to immunising doses of the cocci followed by a dose of lysate (a sequence whose object we do not quite understand). Curiously enough, the condition of this rabbit's kidneys tallied almost exactly with the appearances in kidneys we had found in an animal subjected to repeated doses of scarletinal streptococci plus exotoxin. This animal's kidneys showed naked eye pitting, and microscopically showed focal changes similar to those in Duval's case (see microphotograph // and compare with his microphotograph). As none of our controls had shown anything like similar changes we were at first inclined like Duval to regard them as indicative of the production of chronic lesions by the repeated injections. Subsequently, however, a study of the description of undoubted spontaneous nephritis given by many authors led one to the conclusion that in both Duval's case and ones own a spontaneous type of nephritis had been produced. This, though not necessarily unrelated to the injections, was not a specific result of them; nor was it a phase of a progressive change from the earlier ones observed in acute experiments (see Section on spontaneous nephritis, p. 86).

This opinion, as we shall see, was later clinched by the discovery of another similar kidney from a rabbit first injected only 3 days before.

These various findings with bacteria above recorded form a group most difficult to correlate. It cannot be denied that observers have differed widely. It cannot be maintained that the successes recorded are chiefly with any one type of organism. Interpretation is rendered the more difficult because experimenters have examined kidneys at all possible dates after injection - from a few hours to over a year. Few if any have killed animals at different intervals, and consequently the reader gains comparatively little enlightenment beyond what human cases might furnish, for each observer complacently records the changes at a certain time (the time of death or killing) as the typical changes with the organisms used. Little attention has been paid to the possiblity we are investigating - the possibility of a definite universal sequence of changes in the development of an acute nephritis, the possibility, say, of the incidence of changes being quite different when investigated on the first day and when an animal has lived for a week.

Below, however, we indicate, in tabular form, the situation of the maximum lesions given by the above observers in what have been definitely acute experiments. It will be seen that there is a very considerable concensus of opinion in favour of predominantly glomerular lesions.

Results of Acute Experiments with Bacteria.

Pernici & Scagliosi (131),	chief incidence		glomerulo-tubular.
Lyon (95)	"	"	tubular.
Leecount & Jackson (87)	"	"	glomerular (sometimes nil).
Dick & Dick (37)	"	"	tubular (sometimes a little glomerular).
Coulter & Pappenheimer (30)	"	"	glomerular (followed by suppuration).
Winternitz & Quinby (172)	"	"	glomerular and interstitial.

(Table continued).-

Ophüls (119)	chief incidence		glomerular.
Major (101)	"	"	glomerular, later tubular.
Faber (47)	"	"	glomerular.
Leiter (88)	"	"	nil.
Duval & Hubbard (42)	"	"	glomerular.

Further, the Table indicates that in the only case in which a sequence was looked for it was found (Major) to be glomerular followed by tubular.

The significance and explanation of this will be dealt with after recording our own experiments.

With regard to the attempted production of chronic changes, we do not think that when due allowance has been made for spontaneous nephritis, any success in this respect can be regarded as proved, We except from this conclusion the apparently mechanical action of larger emboli in producing a chronic focal glomerulo-nephritis analogous to that in human endocarditis.

The relation of this condition to ordinary chronic nephritis will be discussed later.

Proteins.

Fairly recently, it has been thought profitable to investigate the results in the kidney of the introduction, usually by injection, of foreign proteins of various kinds. This seems a natural enough line of experiment, in view particularly of modern ideas on cirrhotic conditions of the liver.

Whilst acute changes have in some instances been sought for, and sometimes claimed, it is as a possible key to chronic interstitial nephritis that the subject has been most studied.

In 1913, Longcope (93) claimed to have produced in the rabbit areas of round celled infiltration by repeated injections of horse serum.

Martin and Pettit (104), after feeding rabbits with protein, claimed slight positive results in a large proportion of cases, as also did Valerie (163).

Coulter and Pappenheimer (30) in an article already referred to, also claimed slight changes from the use of egg albumen. Boughton (12) made similar observations.

Newburgh (110) fed rabbits with a high protein diet - chiefly egg white, casein and soya bean. Albuminuria and casts were soon evident. Histologically, acute, subacute and chronic tubular changes resulted, with secondary increase in the interstitial tissue but little change in the glomeruli or other bloodvessels.

Bell and Hartzell (9) attempted similar experiments, but emphasise the possibility of spontaneous changes occurring. The observation is very much to the point, for all the changes noted above are spontaneous in type.

Baldwin (8) attempted to investigate the subject clinically in 23 cases of chronic nephritis. In only 2 could he obtain and verify definite positive reactions to skin tests, but, as he points out, this constitutes neither a confirmation nor a refutation of the relation of foreign proteins to nephritis.

A similar open verdict must meantime be returned on the results of the whole of the experimental work on nephritis with proteins.

Here, for want of a better place, we may make mention of an unusual substance claimed to have been successfully used in the production of nephritis in dogs. Wade (*164*) was investigating an infective (venereal)"sarcoma" of dogs. In the course of his investigations he injected into some dogs a filtrate of the tumour. He claimed in such animals an acute interstitial nephritis, and, later, chronic interstitial change, without, however, any marked glomerular alterations.

Nephritis produced by Products of Intestinal Decomposition.

Somewhat allied to the group of substances we have just been dealing with are the various abnormal products of protein nature which tend to appear in the bowel in intestinal stasis. Such products are now a commonly alleged, indeed a rather fashionable, cause for a variety of chronic diseases, and it is not surprising that their relation to nephritis, at least to chronic nephritis, should have been investigated. Harvey (*59*), using one of these products,- para-hydroxyphenylethylamine, has obtained some interesting results. Some of his rabbits were given the substance orally, others intravenously. Of 33 rabbits, 20 showed changes in the kidneys. These were apparently of the nature of a contraction of the kidney secondary to an atheromatous change in its vessels. The sequence of these changes, as observed by him in different stages, certainly supports this view. In the earliest stages there were atheromatous plaques on the aorta without renal alterations of any kind. Later, a sclerosis of the smaller renal arteries was added to the picture, the kidneys still appearing otherwise normal. In the next stage there was degeneration of the tubular epithelium with dilatation of many tubules and capsular spaces. This progressed, and eventually an increasing round celled infiltration occurred in the interstitial tissue. No advanced changes were described in the glomeruli and one gathers from the article that they suffer only a moderate degree of atrophy of definitely secondary type.

The whole sequence hangs together very well indeed, but it is not certain that all the changes depend upon the atheroma. In spite of its formidable name, it is doubtful if the poisonous molecule is large enough to be retained by the glomerular filter.

If that be correct, tubular changes are to be expected. The interstitial changes may have been of "spontaneous" type, and, as often, merely favoured by the injections.

It must be recalled that spontaneous atheromatous changes are said to be rather common in the vessels of rabbits, although, as a matter of fact, such changes were not present in the rabbits of our series.

We have no note of further work with this or similar substances.

Metals and Organisms.

A number of writers have sought by chemical means to create a preliminary degree of renal damage, and then to inject organisms. The reason for this proceeding is obvious, and lies in the definite difficulty in many cases in getting even acute changes with organisms alone.

Had the elective site of action of the two groups been similar, this method of approach would have been very hopeful. But we believe the elective sites are quite dissimilar, and are consequently not surprised to find the results in this group discouraging.

O'Hare (114) repeatedly injected both uranium nitrate and b. coli into rabbits. The glomeruli showed in some cases dilatation of the capsular spaces, shrinking and thickening of the capsular wall, and occasionally proliferation of the endothelium. There were no arterio-sclerotic changes. There was also a varying amount of scarring in the boundary zone and in the cortex, without much lymphocyte infiltration. O'Hare stated that animals treated with uranium nitrate alone did not show an equivalent degree of scarring. Comparison of his description with that of other workers using uranium alone show, however, that some of these workers have claimed at least as marked changes as he got with b. coli in addition.

Major (102) injected young rabbits repeatedly over a period of a few months with killed cultures of staphylococcus aureus, after a single initial dose of .5 mgm. of uranium nitrate. In 6 of 7 rabbits he found round celled infiltration, diffuse fibrosis, and varying degrees of obstruction and fibrosis of the glomeruli. Such changes were not found with uranium nitrate alone. The same objection applies as to O'hare's observations.

Shaw Dunn (153) noticed incidentally that in his two earliest cases of oxalate nephritis, which were the only two in which streptococci were also injected, more marked changes were found in the glomeruli than in any animals treated with oxalate alone. He does not himself seem to attach any importance to the observation, which is only recorded incidentally, and in any case the tubular changes of the one type of poison, and the glomerular of the other, seem to have been produced independently.

Personal Experiments with Bacteria and their Toxins.

1. Experiments with Streptococcus Scarlatinae (or) (and) its toxins.

A. A series of experiments were done using the exotoxin only. This series consisted of

Rabbits 2,3,4 and 5, and

Rats 1,2,3,4,5,6,7.

Cultures were made from strains of streptococcus scarlatinae obtained from two cases (D1 D2) of scarlet fever at the City Hospital, Aberdeen.

D2 as a rule gave about twice as much toxin as D1. D2 produced about 40,000 skin test doses when incubated for 4 days at 37°C. in 1 % defibrinated blood broth.

Three samples of toxin were prepared.

Toxin No. 1. From D2; grown for 6 days in broth containing 1% defibrinated human blood; filtered through Berkefeld filter A; incubated for 3 days and sterility verified.

Toxin No. 2. From D2; grown for 4 days in broth containing 1/2% defibrinated human blood; filtered through Berkefeld filter F; sterility verified as before.

Toxin No. 3. From D1; grown for 6 days in broth containing 1/2% defibrinated human blood; filtered through Berkefeld filter A; sterility verified as before.

The percentage of blood used was lower than that originally used by Dick and others in the preparation of the toxin, but corresponded with that advocated by Dick in his later papers (39) where he finds that a higher toxic titre is produced with the smaller percentages of blood.

Rabbit 2.

Healthy young rabbit. Weight 1840 grams.
Urine before injection (7 examinations) nil abnormal chemically or microscopically.

12 a.m. 10 c.c. No. 2 toxin intraperitoneally.

7 p.m. dead.

No urine passed since injection. A very small quantity of urine was obtained from the bladder post-mortem and contained no albumen and microscopically no cells or casts.

P.M.

Spleen congested. Weight 1.9 grams.

Right Kidney 8.3 grams. Left Kidney 8.3 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{16.6}{1840} = .009.$

The renal capsules stripped very readily. The cortex was pale. The medulla, particularly the boundary zone, was intensely congested.

The liver appeared to be slightly congested.

The other organs showed no naked eye changes.

Microscopic Examination:-

Liver.-
Showed fat in small quantity in some cells, chiefly in the middle zones of lobules: there was a slight degree of chromatolysis in some of the liver cell nuclei but most of the cells seemed healthy. There was no distinct congestion.

Spleen:-
Intense congestion.

Kidneys:-
The glomeruli were greatly congested and distended. The nuclei of the endothelium of the capillaries were swollen and pale and often deformed, with partial block of the lumen here and there. Here and there, too, there was complete necrosis of individual loops of tufts, with disappearance of the endothelial nuclei. There was a little round celled infiltration of the tufts, but only a very few polymorphs were present. Intercapillary

haemorrhages were numerous. The epithelium covering the tuft was swollen and at places it was lost. This loss of epithelium was at times accompanied by extravasation of a few R.B.C. into the overlying part of the capsular space. The epithelial deficiency seemed to be marked only where there was either great distension or local necrotic change in the portion of the tuft immediately underlying it. In only very few cases were desquamated epithelial cells found lying free in the capsular space.

There was albuminous exudate in most of the capsular spaces, mainly on the parietal aspect. The capsular spaces were dilated, and, as above mentioned, a few contained R.B.C.

Congestion of the organ was marked particularly in the medulla, and most of all in the boundary zone. In this zone there were numerous small haemorrhagic areas within which there was considerable round celled accumulation, haemorrhages between the tubules, and catarrh of the enclosed tubules.

There was no change in the interstitial tissue elsewhere.

Outside these few small areas, there was only very slight tubular change. The convoluted tubules showed only very slight catarrh, with, however, commencing karyolysis in many parts. There was slight vacuolation of some cells. No casts were seen.

The tubular changes were not nearly so striking as the glomerular. There was no change in the tubules outside the convoluted tubules (save in the small haemorrhagic areas already noted).

There was no fatty change anywhere.

Summary.

Marked endoglomerular changes, fairly marked epiglomerular changes: slight tubular changes.

Rabbit 3.

Healthy young rabbit. Weight 1970 grams.
Urine before injection (5 examinations) nil abnormal chemically or microscopically.

12 a.m. (6/10/25) 8 c.c. No. 3 toxin intraperitoneally.

6/10/25. 5 p.m. Urine nil abnormal chemically or microscopically.

12 a.m. (9/10/25) Urine nil abnormal chemically or microscopically.
5 c.c. No. 1 toxin and 5 c.c. No. 2 toxin intraperitoneally.

10/10/25. Died early this morning.

P.M.

A very small amount of urine in the bladder showed a trace of albumen to the nitric acid test. Microscopically, it showed fairly numerous epithelial cells and one or two hyaline casts.

Spleen:
1.3 grams. Congested.

Kidneys:-
Were like those of rabbit 2 but there was more congestion; the boundary zone of the medulla showed a broader band of deep congestion, and the cortex was also more obviously congested.

Right Kidney 7.63 grams. Left Kidney 8.08 gms.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{15.71}{1970} = .009.$

Liver:-
Nil abnormal naked eye.

Nil abnormal in other organs naked eye.

Microscopic Examination:-

Kidneys:-
The glomeruli were markedly congested and the endothelium of the tuft was greatly swollen. The endothelial nuclei were swollen and pale and the lumen of many capillaries was reduced or completely obliterated. In some tufts there were small numbers of infiltrating small round cells. Here and there tufts showed localised necrosis of a loop or loops,

usually of a superficial loop. The capsular spaces of the more affected glomeruli contained albuminous exudate, either adherent to the parietal aspect, or gumming portions of the tuft to that aspect. Frequently the epithelium was extensively denuded from the surface of the tuft, and where it was not, it was very prominent. A few epithelial nuclei were lying free in the capsular spaces, which also contained occasionally one or two R.B.C.

The parietal epithelium was rather prominent, but was not so swollen as the epithelium covering the tuft.

Though the glomeruli were not all equally affected, almost all showed in some degree the major changes described.

All the vessels of the kidney were greatly congested.

In the boundary zone and to a lesser extent in the cortex there were a few small focal increases of cellularity between tubules. These areas were greatly congested. The cells were for the most part mononuclear round cells, often rather large, but there were a few polymorphs. The tubules between which they lay were catarrhal. The congestion and the polymorphs indicated an acute change but it is quite possible that these areas and the similar ones in rabbit 2 represented the acutely inflamed scars of pre-existing slight lesions of spontaneous nephritis. There was no general interstitial change.

The nuclei of the epithelial cells of the tubules in the cortex stained well. There was no breakdown of epithelial cells, but there was a little albuminous material in the lumen of a few tubules here and there. Frozen sections showed some cloudy swelling of the broad part of the ascending limb of the loop of Henle and to a very slight extent of the convoluted tubules.

There was marked deposit of fat throughout the whole of the broad part of the ascending limb of the loop of Henle in the boundary zone. There was a very little fat in occasional cells of the convoluted tubules (near the base of the cell).

There was no fat in the glomerulus or elsewhere save as just mentioned. Nothing abnormal was noted in the collecting tubules.

Summary.

Marked endoglomerular changes, pretty marked epiglomerular changes: slight tubular and interstitial changes. (The tubular changes though slight were a little greater than those in rabbits 2,4 and 5 which were subjected to a single injection only).

Rabbit 4.

Healthy young rabbit. Weight 1440 grams.
Urine before injection (5 examinations) nil abnormal chemically or microscopically. (In this and other rabbits' urine a structure was frequently noted microscopically which might easily have been mistaken for a cast. It consisted of a cylinder of mucus coated with granular inorganic debris - phosphates etc.)

11.45 a.m. 2 c.c. No. 3 toxin intraperitoneally.

Died same night at 6 p.m.

P.M.

No urine in bladder and none apparently passed since injection.

Right Kidney 6.4 grams. Left Kidney 6.4 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{12.8}{1440} = .009.$

Spleen:-

1.6 grams. Congested.

The naked eye appearances of the kidneys were similar to those of the kidneys of rabbits 2 and 3.

The other organs showed nil abnormal to naked eye examination.

Microscopic Examination:-

Liver:-

Slight cloudy changes: nil abnormal otherwise.

Spleen:-

Congestion.

Kidneys:-

The glomeruli showed great congestion. The endothelial cells of the tuft were greatly swollen with

consequent narrowing of some capillaries. There was some infiltration of some of the tufts, chiefly with small round cells, though there were a few polymorphs occasionally. The tuft epithelium was exceedingly swollen and prominent, where present. In many cases it was absent or cells of it were lying free in the capsular space. The majority of the capsular spaces were distended, and nearly all contained some vacuolated albuminous material, adherent in crescentic form to the parietal aspect of the capsule or stretching from the parietal capsule to some projecting portion of the tuft. The parietal epithelium was very prominent also. A few R.B.C. were present in one or two capsular spaces.

All vessels were congested especially the intertubular plexus.

The interstitium showed nothing of note.

The tubules were less affected than the glomeruli but here and there seemed to be some degeneration of the nuclei, with partial karyolysis and the lumen of many of the tubules contained a trabecular vacuolated albuminous material like that in the tuft capsular spaces.

No casts were seen.

No fatty change was visible anywhere in the tubules, but there was slight fatty change in the capillary walls in some tufts, and also in some capillary vessels of the intertubular plexus.

Summary.

Marked endoglomerular changes, pretty marked epiglomerular changes: slight tubular and interstitial changes. ~~(The tubular changes though slight were a little greater than those in rabbits 2 and 3).~~

Rabbit 5.

Healthy young rabbit. Weight 1440 grams. Urine before injection (5 examinations). In good quantity daily. No albumen to boiling or nitric acid tests. Nil abnormal microscopically.

11.45 a.m. 2 c.c. No 3 toxin intraperitoneally.

Died 6 p.m. same night.

No urine obtained after injection or found in the bladder post-mortem.

Right Kidney 6.65 grams. Left Kidney 6.55 grams.

Spleen 1.05 grams. Congested.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{13.20}{1440} = .009$.

Liver:-
Nil abnormal.

Kidneys:-
The kidneys appeared to the naked eye like those of rabbits 2,3, and 4. Nil abnormal in other organs.

Microscopic Examination:-

Liver:-
Slight cloudy swelling.

Spleen:-
Congestion.

Kidneys:-
The glomerular changes were similar to those in previous rabbits, perhaps tending to be more intense with rather more necrosis. Some of the capillary loops showed thrombosis.

The tubular changes were rather more severe than in the previous single injection experiments (rabbits 2 and 4) but less severe than in rabbit 3 where the two injections had been given and the animal had survived longer.

The majority of the nuclei of the convoluted tubules stained well but a minority showed faint staining and swelling or alternatively pyknosis. There was very little catarrh.

It was in the thick parts of the ascending limbs of the loops of Henle that more marked changes were seen. These sometimes showed considerable catarrh, with widespread necrosis of the epithelial cells.

There was albuminous material in some of the collecting tubules and in some of the duct of Bellini, although the lining of these structures was healthy, and, similarly, there was some albuminous material in some convoluted tubules just as they left the capsular space. Most of such albuminous material merely formed a network in the lumen but in the ducts of Bellini some of it was in the form of fully formed casts.

There was congestion of all vessels of the organ and no special changes in the interstitium.

Fat was present in the broad part of the ascending limb of the loop of Henle, and there only.

Microphotograph 6

Summary.

Marked endoglomerular changes, pretty marked epiglomerular changes: slight tubular and interstitial changes.

The next experiment is the first we have to record of a number in which the method of injection was designed expressly with a view to the ultimate production, if possible, of chronic lesions. As the animal in the present instance lived only 11 days after the first injection, the scheme was not properly tested in it, but the rationale of the voluminous dilute injections will be explained now.

Unquestionably, the chief difficulty in experimental nephritis has been to sustain the initial lesions and intensify them to the point of production of permanent damage, particularly of permanent glomerular damage, and of permanent renal insufficiency. The ordinary method of repeated injections resembles very closely that used by bacteriologists with the same animals to induce immunity, sometimes, as with diphtheria toxin, an immunity of very high degree. This is scarcely what an experiment on chronic toxaemia requires. It would be desirable if possible to devise a method by which the animal would not be able to respond by an efficient immunising process. Only too often, after the subsidence of acute changes, the animal completely recovers, and fails to react, (or rather reacts perfectly) to subsequent injections and when killed shows a practically normal kidney; or, if in the desire to "mak siccar" and secure definite changes, a final large dose which turns out to be lethal is given, the picture is that of acute nephritis in a previously healthy kidney. Now, in man, it is not probably an identical state of affairs to this that leads to a chronic nephritis. It is more likely that a varying but fairly continuously sustained septic absorption is proceeding from some hidden focus, and that the immunity reactions, though present in some degree, are insufficient to neutralise the poison entirely and so prevent progressive changes in, amongst other organs, the kidneys. One of the possible methods of simulation of this natural process is by a constant instillation of toxin. This has been tried, with, it must be admitted, very unconvincing results, by Jes Jessen (*67*). His article was brought to the writer's notice by Professor Shennan and one intended to repeat similar experiments, but for several reasons had to modify Jessen's technique. For one thing, the Home Office, after considerable correspondence, refused a licence for the purpose. A study of the details of Jes Jessen's paper reveals more important considerations however. Jes Jessen, by a sterile siphonage apparatus introduced dilute poisons of chemical or bacterial origin into the tissues of rabbits (subcutaneously, intraperitoneally or intravenously in different cases). The rabbits were in very confined

cages for the 4 hours of the instillation, which was repeated daily (or less frequently). A little consideration will show that the method was not really a continuous one, and that quite a sudden fall occurred at the end of 4 hours, and that at least a 20 hour gap intervened between every two injections. The injections were deliberately given at such a rate that no accumulation of fluid occurred in the tissues. Whilst a slightly lesser degree of discontinuity was achieved than by single daily injections, it appeared that a greater uniformity of absorption could be secured in several ways - which would be covered by the conditions of an ordinary licence.

In the first place it was noted by actual experiment that if a considerable volume of fluid were injected into the rabbit's peritoneal cavity (as in this experiment), quite a number of hours, sometimes 24, might elapse before its complete absorption. This seemed to render possible a fairly continuous administration.

In other experiments, such as the one which follows, small hourly injections were given during the day, and the effect prolonged as much as possible by making the last dose of the day a larger one, and injecting it in a very dilute form into the peritoneal cavity.

Rabbit T.

Healthy rabbit. Weight 1045 grams.
Urine before injections (4 examinations) Nil abnormal chemically or microscopically.

26/7/26. Between 10 a.m. and 5 p.m. at intervals (approximately hourly) a total of 80 c.c. saline containing .003 unit diphtheria toxin intraperitoneally.

27/7/26. Between 9 a.m. and 6 p.m. at hourly intervals a total of 70 c.c. of (hypertonic) saline intraperitoneally, containing .0015 unit diphtheria toxin.
Then at 6 p.m. 50 c.c. hypertonic saline intraperitoneally containing also .0015 unit diphtheria toxin.
(Total in day = .003 D.T.)

28/7/26. Between 9 a.m. and 5 p.m. a total of 60 c.c. of hypertonic saline intraperitoneally, the last and biggest dose at 5 p.m. Total amount of toxin given during the day = .003 unit diphtheria toxin.

29/7/26. Between 9 a.m. and 5 p.m. a total of 100c.c. of hypertonic saline intraperitoneally, the last and biggest dose at 5 p.m. Total amount of toxin given during day= .003 unit diphtheria toxin.

30/7/26. Between 9 a.m. and 5 p.m. a total of 100c.c. of hypertonic saline intraperitoneally, the last and biggest dose at 5 p.m. Total amount of toxin given during day= .0015 unit diphtheria toxin.

5/8/26. 11 a.m. 2 c.c. No. 3 Strep. Toxin intraperit.

6/8/26. Found dead and cold in morning.

P.M.

Right Kidney:- 5.7 grams. Left Kidney:- 5.8 grams.

$$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{11.5}{1045} = .011$$

No naked eye changes were seen in the kidneys beyond a little swelling and intense congestion.

Spleen:-

Soft, purple, of normal size.

Liver:-

Congested.

Microscopic Examination.

Liver:-

Congested.

Spleen:-

Very congested; excess of pigment in prominent endothelials of pulp; Malpighian bodies prominent.

Kidneys:-

The changes to some extent combined the appearances seen in the streptococcal toxin kidneys already described with those in diphtheria toxin poisoning yet to be described. As the incidence of the two falls on the same structures and follows a similar sequence, it is natural that somewhat more severe damage should be noted here than with either alone.

There was no evidence of any commencing chronicity due to the earlier diphtheria toxin injections, and it appeared simply that acute changes caused by these had not been completely recovered from, when the fatal dose of streptococcal toxin was given.

The glomeruli showed very marked alterations indeed. All were exceedingly congested, but portions of most, and the whole of some, were completely necrotic. In such necrotic areas there was merely a fine fibrin-impregnated network outlining the capillary walls, and nuclei were entirely absent.

There was no definite cellular infiltration

anywhere in the tufts. All the endothelial nuclei were either swollen or undergoing karyorrhexis (save a few which showed pyknosis). Between capillaries there was a certain amount of fibrinous material. Numerous dilated loops had broken down into one another, and sometimes a portion of a loop was occupied by a "blood-cyst" containing a uniform fibrinous coagulum with sometimes one or two degenerating endothelial nuclei. In one or two cases the whole tuft was practically replaced by such an appearance. The epithelium over the tuft was at places wanting but its presence over some badly disorganised tufts was quite a striking feature. Sometimes the peripheral portion of a tuft had simply disappeared, leaving a ragged edge to the remainder. In one or two such sites the related first convoluted tubule contained some R.B.C. at its commencement.

Sometimes the capsular spaces contained a little albuminous material. Occasionally there was albuminous material on the surface of the tuft but under the epithelium.

Occasionally only a haemorrhagic area containing a few nuclei represented the glomerulus and its capsules.

Notwithstanding these striking glomerular changes, the tubules showed merely a slight catarrh here and there with partial karyorrhexis of occasional nuclei. The first convoluted tubules as they left the capsular space, some of the other convoluted tubules, and many collecting tubules, contained hyaline casts.

All vessels of the organ were greatly congested.

Fat:- None seen anywhere.

Microphotograph, 7.

Summary.

Very marked endoglomerular changes, marked epiglomerular changes: slight tubular changes, no interstitial changes.

The remaining experiments of those in which the exotoxin of streptococcus scarletinae was used alone were performed with rats. They were not nearly so susceptible as the rabbits, and the changes found were correspondingly less marked.

We were in doubt as to whether it was necessary to record the protocols in full, but decided to do so, although little reference will be made to them subsequently. They tend, however, as far as they go, to confirm the results obtained with the rabbits, and for this reason are included.

Rat 1.

Healthy rat. Weight 180 grams.
Urine before injections (6 examinations) nil abnormal chemically or microscopically.

6/10/25. 2 c.c. No. 1 strep. toxin intraperitoneally.

Nil abnormal in urine at any date before next injection.

9/19/25. 8 c.c. No. 1 Strep. toxin intraperitoneally.

10/10/25. Urine trace of albumen to nitric acid test.

Micro:- R.B.C., leucocytes and epithelial cells.

12/10/25. Urine trace of albumen to nitric acid test.
Micro:- R.B.C.

13/10/25. Almost complete anuria for last 24 hours (1 c.c. of urine which showed a fair amount of albumen).
12 c.c. No. 3 toxin intraperitoneally.

14/10/25. Very ill. Urine 5 c.c. Fair amount of albumen to nitric acid test.
Micro:- A fair number of epithelial cells and a few hyaline casts.

15/10/25. Rat found dead in morning. 5 drops of urine loaded with albumen.
Micro:- epithelial cells and casts.

P.M.

Spleen .46 grams.

Right Kidney .81 gram. Left Kidney .79 gram.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.60}{180} = .009.$

The cortex and boundary zone were congested. The capsule stripped readily and left a smooth surface.

Liver:-
Congested.

Microscopic Examination:-

Spleen:-
Much phagocytosis of R.B.C. and pigment in pulp and endothelial cells. Many sinusoids showed a wall practically lined by pigment-loaded endothelial cells. Congestion marked. Mapighian bodies of average prominence.

Liver:-
Congestion. A little fat in some cells at the periphery of the lobules.

Kidneys:-
The glomeruli were congested and in some cases showed apparently increased cellularity, with an increase chiefly of fibroblastic nuclei. The epithelium covering the tuft was in places deficient. The tubules were in some cases normal, in others showed a varying degree of change, in some fairly marked. Many of the cells were vacuolated and some debris in the lumen of others was apparently the remains of such vacuolated cells. There was catarrh in some tubules. Many tubules showed some cloudy swelling of their cells. There were hyaline casts in the lumen of some tubules. Fatty degeneration was present in fair degree chiefly in the form of minute droplets in the basal parts of the cells of the convoluted tubules; there was also a little fatty degeneration in one or two of the glomeruli.

Summary.

Quite a distinct amount of change; pretty marked tubular changes, rather less marked glomerular changes.

Rat 2.

Healthy rat. Weight 190 grams.
Urine before injection (4 examinations) albumen thrice negative to nitric acid test, but on one occasion one or two epithelial squames and leucocytes were found microscopically, and a questionable trace of albumen to the nitric acid test.

16/11/25. 11.30 a.m. 5 c.c. No. 1 strep. toxin intraper.

5 p.m. Died. No urine obtained post-mortem.

P.M.

No peritonitis. Kidneys and Spleen congested. No other naked eye lesions.

Right Kidney .82 gram. Left Kidney .87 gram.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.69}{190} = .009.$

Spleen .68 gram.

Microscopic Examination:-

Spleen:-

Congestion and increased pigment.

Liver:-

Congestion and small haemorrhages here and there in the lobules, with necrosis of a few liver cells; here and there small patches of polymorph infiltration.

Kidneys:-

The glomeruli showed slight swelling of the endothelial cells and perhaps a little increase in cellularity. A few infiltrating polymorphs were noted and some round cells. The tufts were congested but this was masked by the swelling of the endothelials and consequent narrowing of capillaries. The glomeruli almost completely filled up the capsular space. One or two necrotic loops were noted in glomeruli. In one capsular space a few R.B.C. were noted, and there were globules of albumen in a number of others.

Some of the glomeruli showed no alteration save congestion. Thrombosis was present in a few loops of some tufts. The epithelium covering the less affected tufts was normal, that over the more affected was in part gone or represented by occasional

swollen cells in the capsular space.

When the epithelium looked normal there was never any albumen in the capsular space.

All the vessels of the cortex were congested. Otherwise no interstitial change was noted. (Frozen sections showed a little oedema of the interstitial tissue).

There was fairly marked but rather patchy cloudy swelling in the convoluted tubules, and karyolysis was commencing in some of the epithelial nuclei there. No casts were seen.

No change was seen in the medulla save congestion of the vessels.

There was no fat anywhere.

Summary.

Changes of very mild degree - glomerulo-tubular. The glomerular seemed rather the more marked, and the absence of casts and other indications of a considerable albuminuria is apparently to be correlated with the absence of extensive damage to the epithelium covering the glomerular tufts.

Rat 3.

Healthy rat. Weight 160 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

23/11/25. 12 a.m. 3/4 c.c. No. 3 toxin intraperitoneally.

5 p.m. Died.

P.M.

Urine 1 c.c. or less. Albumen negative to nitric acid test. Micro:- No cells or casts.

Liver, Spleen and Kidneys appeared congested. Nil otherwise abnormal, naked eye.

Spleen .79 gram.

Right Kidney .81 gram. Left Kidney .79 gram.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.60}{160} = .010$

Microscopic Examination:-

Liver:-

Congested. Petechial haemorrhages with focal necrosis of liver cells, especially in intermediate and central zones of lobules. No fat.

Spleen:-

Considerable congestion. Malpighian bodies fairly prominent. Pulp congested and cellular; a considerable amount of pigment.

Kidneys:-

The endothelial nuclei of the glomeruli were greatly swollen and there were a certain number of infiltrating round cells with an occasional polymorph. The epithelium covering the tufts was usually intact, but was gone in places overlying areas of fairly marked change within the tufts.

In the capsular spaces of the more affected tufts, there was a little albuminous material or sometimes a few R.B.C. There was, however, great variation in the degree of affection of different tufts.

There were casts in one or two convoluted tubules. These tubules showed widespread but very slight cloudy swelling with some vacuolation of the tips of the cells, but no further degenerative changes. The cortex was markedly congested.

No fatty change was evident anywhere.

Summary.

The changes found are again of mild degree - glomerulo-tubular, with the more significant changes glomerular. The glomerular changes are chiefly endo-glomerular and only to a lesser extent is the epithelium of the tuft affected.

Rat 4.

Healthy rat. Weight 156 grams.
Urine before injection (5 examinations) nil abnormal chemically or microscopically.

30/11/25. 12 a.m. 1/2 c.c. No. 3 toxin intraperit.

1/12/25)
2/12/25) Urine nil abnormal chemically or micro.
3/12/25)

3/12/25. 3.30 p.m. 1/2 c.c. No. 3 toxin intraper.

4/12/25)
5/12/25) Urine nil abnormal chemically or micro.
6/12/25)
7/12/25)

7/12/25. 4 p.m. 1/2 c.c. No. 3 toxin intraperit.

8/12/25. Urine trace albumen to nitric acid test.
Micro:- Nil abnormal.
12 a.m. 1/2 c.c. No. 3 toxin intraperit.

10/12/25. Urine trace of albumen to nitric acid test.
Micro:- Nil abnormal.

11/12/25. Found dead in morning. (P.M. Urine - faint trace of albumen to nitric acid test.
Micro:- Nil abnormal).

P.M.

Kidneys a little enlarged and congested.

Right Kidney .71 gram. Left Kidney .72 gram.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.43}{156} = .009.$

Spleen rather congested and Malpighian bodies prominent.

Liver congested.

Nil otherwise abnormal naked eye.

Microscopic Examination:-

Spleen:-
very distinct congestion. Malpighian bodies prominent. Blood pigment in great excess.

Liver:-
No important change.

Kidneys:-
The glomeruli were congested. Here and there there was epithelial loss and escape of a few R.B.C. into the capsular space, but this change was not extensive. The cellularity of the tufts was not distinctly increased, but the endothelial nuclei were faint and polymorphs were present in appreciable though small numbers. Sometimes there were small areas of necrosis in tufts.

The convoluted tubules showed slight cloudy change and occasionally a little catarrh. Sometimes the epithelial nuclei were a little pyknotic. Nil abnormal noted in other tubules.

No interstitial changes were detected.

No fat was present anywhere.

Summary.

Very mild changes; glomerulo-tubular.

Changes in the glomeruli slightly the more distinct.

Rat 5.

Healthy rat. Weight 180 grams.
Urine before injection (2 examinations) nil abnormal chemically or microscopically.

14/12/25. 3 p.m. 1/2 c.c. No. 3 toxin intraperit.

15/12/25)
16/12/25) Urine nil abnormal chemically or micro.
17/12/25)
18/12/25)

18/12/25. 11 a.m. 1/2 c.c. No. 3 toxin intraperit.

19/12/25)
21/12/25) Urine nil abnormal chemically or micro.

21/12/25. 12 a.m. 1 c.c. No. 3 toxin intraperit.

22/12/25) Urine, a faint trace of albumen to nitric acid
23/12/25) test; nil abnormal microscopically.
24/12/25)

No examinations were made thereafter till -

31/12/25. Urine, albumen faint trace to nitric acid test. Micro:- Nil abnormal.

2/1/26. Urine, albumen negative to nitric acid test. Micro:- Nil abnormal.

4/1/26. Urine, albumen doubtful trace to nitric acid test. Micro:- Nil abnormal.

11 a.m. 2 c.c. No. 3 toxin intraperit.

5/1/26.)
6/1/26.) Urine nil abnormal chemically or micro.

6/1/26. 11 a.m. 2 c.c. No. 3 toxin intraperit.

7/1/26. Rat found dead in morning.

P.M. Urine:- A very few epithelial (rounded) cells; some squames; no casts - urine obtained from penis by bladder compression.

P.M.

Right Kidney .81 gram. Deeply congested throughout, especially in boundary zone of medulla and in cortex.

Left Kidney .86 gram. Appearances similar.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.67}{180} = .009$

Spleen 1.29 grams. Deeply congested.

Liver congested.

Nil abnormal noted in other organs.

Microscopic Examination:-

Liver:-
Areas of necrosis and haemorrhage, chiefly towards the centre of lobules; some congestion; here and there patches of polymorph infiltration between liver cells; no fat present.

Spleen:-
Pulp congested; pigment increased: Malpighian bodies fairly prominent.

Kidneys:-
The glomeruli were congested. The capsular spaces occasionally contained a little albuminous exudate or a few R.B.C. The epithelial covering of the tuft was occasionally incomplete. The capillary walls were swollen by infiltration with finely fibrillated connective tissue - almost hyaline. This had in many cases led to block of a number (even occasionally of the whole) of the capillaries of the tufts. The number of nuclei in the tuft was not distinctly increased, but the percentage of polymorphs was raised, and the connective tissue cells instead of being nearly round were often elongated.

Occasionally there was slight adhesion of the tuft to the capsular wall.

The convoluted tubules and the broad part of the ascending limb of the loop of Henle showed some catarrh and pretty marked degeneration of nuclei which were often faint or small, and occasionally absent.

In addition, there was a patchy increase of cellular connective tissue just here and there in the cortex. (Slighter appearances of this kind had been seen in one of the controls, and the significance which is to be attached to these is consequently doubtful).

The cells in these accumulations seemed to be mainly round cells, but some were commencing to elongate

towards a spindle shape. There were a few polymorphs along with them. There was little fully formed connective tissue and the process appeared to be fairly recent. Only a minority of the patches were around glomeruli, but all were in the cortex. Such tufts as were included were overcellular, and were for the rest filled with the fine fibrillar connective tissue already mentioned, practically no capillary lumen being present in these cases. The tufts were not contracted, however, and only slight local adhesion had occurred, and no markedly shrunken or hyaline glomeruli were seen in any patch. All patches, however, contained shrunken and atrophic tubules (often, as said, without any glomeruli - at least in the part cut across in the section).

No fat was present anywhere in the organ.

Summary.

Slight subacute glomerular changes, with commencing fibrosis in the glomeruli. Some degenerative change in many tubules, with, in a few patches, atrophic changes associated with cellular infiltration of the surrounding connective tissue.

We are not certain that all the changes described were due to the injections.

Rat 6.

Healthy rat. Weight 157 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

18/12/25. 11 a.m. 1/2 c.c. No. 3 toxin intraperit.

19/12/25. Urine nil abnormal chemically. Micro:- A few leucocytes.

21/12/25. Urine, albumen trace to nitric acid test. Micro:- Nil abnormal.

11 a.m. 3/4 c.c. No. 3 toxin intraperit.

22/12/25)
23/12/25)
24/12/25) Urine nil abnormal chemically or micro.
31/12/25)
2/1/26)
4/1/26)

4/1/26. 11 a.m. 1 c.c. No. 3 toxin intraperit.

5/1/26)
6/1/26) Urine nil abnormal chemically or micro.

6/1/26. 11 a.m. 2 c.c. No. 3 toxin intraperit.

7/1/26. Urine nil abnormal chemically or micro.

8/1/26. Urine.albumen doubtful to nitric acid test. Micro:- One or two epithelial cells, no casts.

9/1/26. Urine nil abnormal chemically or micro.

11/1/26. Urine, albumen doubtful to nitric acid test. Micro:- Nil abnormal.
11 a.m. 2 c.c. No. 3 toxin intraperit.

12/1/26)
13/1/26)
14/1/26) Urine nil abnormal chemically or micro.
15/1/26)
16/1/26)
18/1/26)

18/1/26. 5 p.m. 3 c.c. No. 3 toxin intraperit.

19/1/26)
20/1/26) Urine nil abnormal chemically or micro.
21/1/26)

21/1/26. 5p.m. 3 c.c. No. 3 toxin intraperiton.

22/1/26)
23/1/26) Urine nil abnormal chemically or micro.
25/1/26)
26/1/26 Urine, trace of albumen to nitric acid test.
Micro:- Nil abnormal.
27/1/26 Urine, trace of albumen to nitric acid test.
Micro:- Nil abnormal.
5 p.m. 3 c.c. No. 3 toxin intraperit.

28/1/26. Urine, nil abnormal chemically.
Micro:- A few epithelial cells, no casts.

29/1/26)
1/2/26)
2/2/26)
4/2/26) Nil abnormal chemically or microscopically.
5/2/26)
8/2/26)
10/2/26)

10/2/26. Killed.

P.M.

Spleen:- Congested. Prominent Malpighian bodies. Wt. .77 grams

Right Kidney .66 gram. Left Kidney .64 gram.
Nil abnormal in kidneys naked eye.
No change noted in other organs.

Microscopic Examination.

Spleen:-
Slight congestion of pulp. Malpighian bodies more prominent than in any animal of series so far examined.

Kidneys:-
The glomeruli were slightly congested. Here and there, there was a little albuminous exudate into a capsular space. There was a little cellular connective tissue proliferation round a few glomeruli, and commencing adhesion of anumber of the glomeruli to the capsule. The epithelium covering the tuft was atrophied but present. The number of nuclei in the tufts was slightly increased, but the really distinct feature was their alteration in shape. In place of round nuclei, which were found in the tufts even in some controls, the nuclei here were irregularly elongated, and even

short spindle shaped, and a deposit of connective tissue had commenced in the tuft, in varying but slight degree.

There was no congestion outside the glomeruli.

There was a very slight increase of connective tissue throughout the cortex.

The tubules showed no cloudy swelling or other change.

Summary.

The changes are again of mild degree. They are fairly chronic and are glomerular, with minor interstitial changes.

Rat 7.

Healthy rat. Weight 161 grams.
Urine before injections (4examinations) nil abnormal chemically or microscopically.

11/1/26. 11 a.m. 3/4 c.c. No. 3 toxin intraperit.

12/1/26. Urine, albumen doubtful to nitric acid test. Micro:- One or two epithelial cells and leucocytes, no casts.

13/1/26.)
14/1/26.) Urine nil abnormal chemically or micro.
15/1/26.)

16/1/26. Urine, a trace of albumen to nitric acid test. Micro:- Nil abnormal.

18/1/26. Urine nil abnormal chemically or micro.
4 p.m. 1 c.c. No. 3 toxin intraperit.

19/1/26. Urine, a trace of albumen to nitric acid test. Micro:- One hyaline cast, otherwise nil abnormal.

20/1/26. Urine nil abnormal chemically or micro.

21/1/26. Urine, a trace of albumen to nitric acid test. Micro:- Nil abnormal.
5 p.m. 2 c.c. No. 3 toxin intraperit.

22/1/26. Urine, a faint trace of albumen to nitric acid test. Micro:- Nil abnormal.

23/1/26.)
25/1/26.) Urine nil abnormal chemically or micro.
26/1/26.)

27/1/26. Urine, a doubtful trace of albumen to nitric acid test. Micro:- Nil abnormal.
4 p.m. 2 c.c. No. 3 toxin intraperit.

28/1/26.) Urine nil abnormal chemically or
29/1/26.) microscopically.
1/2/26.)
2/2/26.)
3/2/26.)
4/2/26.)

5/2/26. Urine, a faint trace of albumen to nitric acid test. Micro:- Nil abnormal.

8/2/26. Urine nil abnormal chemically or micro.

10/2/26. 11 a.m. Killed.

P.M.

Spleen congested. Wt. .61 gram.

Kidneys and other organs nil to note naked eye.

Right Kidney .78 gram. Left Kidney .70 gram.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.48}{161} = .009.$

Microscopic Examination:-

Liver.
No definite alteration.

Spleen:-
Not much congestion. Reticulum rather increased. Malpighian bodies rather prominent but contained a rather excessive connective tissue stroma.

Kidneys:-
The glomeruli showed very slight congestion. Some capillaries were dilated though empty. The tufts were mostly rather large and almost filled the capsular space. A little albuminous exudate was present in a few capsular spaces and the visceral epithelium, while generally intact, occasionally showed slight deficiency, particularly in the albumen-containing spaces.

In addition to the endothelial cells the tufts showed a fair number of small round cells and some polymorphs. As a few of these were seen in controls their significance is doubtful.

There was no increase of connective tissue in the tufts.

No catarrh was visible in the tubules, which were practically normal.

Summary.

Very slight glomerular change is the most that can be said, and, in view of the approximation of some controls to the appearances here, even that is doubtful.

Discussion of Changes Induced by Scarlatinal Streptococcus Exotoxin.

The changes found in rats and rabbits were of a similar type, but those in the rabbits were the more distinct and the more severe.

We can deal with and dismiss the rat experiments briefly. They show, in less convincing degree, the same incidence and sequence as we shall trace in the rabbit experiments.

As they were less susceptible to the toxin, rats were more suited for observing the results of repeated dosage. These were not very convincing. The lesions were slight and not distinctly beyond the conceivable range of variability due to other causes, in animals which might show a trace of albuminuria before injection. There appeared to be a tendency for repeated injections to cause an increase in the number of fibroblasts in the tufts, and even some adhesion of the tufts to the capsules. The interstitial changes were not distinctly greater than in controls. It is probable, though not certain, that the repeated acute damage (which was chiefly glomerular) had caused a little more alteration than was consistent with complete anatomical recovery, and that the fibroblastic multiplication was the indication of this. If that be true, it is not surprising that coexisting interstitial changes were not found, for the acute condition spares the interstitium. Interstitial change would, one might expect, be a later feature in the sequence, depending in turn on the glomerular alterations and not on primary acute interstitial damage.

It is with regard to the acute changes that we are given definite information and that information is best provided by the r abbit experiments.

These rabbits' kidneys were always greatly congested throughout. Microscopically, the most marked changes were in the glomeruli. Alterations in the tubules were less constant and less severe.

The glomerular changes showed a definite sequence. Case after case showed that the lesser affected glomeruli showed changes almost confined to the capillaries and the tissue between them. Some

tufts with quite a considerable amount of endoglomerular change showed only a little swelling of the covering epithelium. When, however, one turned to still more severely affected tufts - to tufts within which there was definite necrosis of loops, disintegration of portions etc. etc., the covering epithelium was found to be more severely affected - greatly swollen, and detached in places. Coincidently with this change, albuminous material and even occasionally R.B.C. appeared in the capsular spaces.

In tufts where the epithelium still retained its integrity, it could occasionally be noted that within the tufts there were intercapillary collections of albuminous exudate, or even sub-epithelial albuminous exudate, although no albumen was present in the capsular space.

Round celled infiltration formed quite a subsidiary feature of the degenerative glomerular changes, and it was the absence of any considerable cellular infiltration that best distinguished the condition from glomerular nephritis as seen in man. The difference seems to be probably an indication that usually in man the causal organism as well as the toxin is present in the tufts.

The sequence just described is one which fits in exceedingly well with our previously expressed views as to the differing modes of action of crystalloid and colloid poisons. Instead of getting the earliest changes in the tubules we get them in the glomeruli. Further, the earliest changes are clearly endoglomerular. When a raised, glomerulus-damaging, dose of crystalloid was given, it was difficult to tell whether the epithelium or the endothelium of the tuft suffered most, but the impression was that the former was rather the more severely affected. Here the process is very distinctly reversed.

Now, a toxic substance which does not filter through the healthy glomerular endothelium and epithelium will be greatly concentrated in the glomerular capillaries by the loss of fluid into the filtrate. We are dealing with no trivial loss of fluid, but with a very considerable one indeed (possibly, as in Cushny's experiment, 120 times the urine passed in any period considered). The heavy endoglomerular incidence is explained in this way. The tubules are not exposed to the same increased concentration for the toxic plasma in the intertubular plexus is speedily re-diluted by the fluid reabsorbed from the tubules (in Cushny's

experiment, 119/120ths of the original filtrate.) Thus we would expect exactly what we find: - changes in the tubules are not absent, but they are similar in degree to those in highly differentiated cells elsewhere (e.g. the polygonal cells of the liver).

The only exception in the rabbits to this extreme mildness of the tubular changes is rabbit 3, where a later stage is represented, for two injections were given. Rat 1 also represents a later stage and similarly shows more severe tubular lesions. (Other rats either r epresent earlier stages, or definitely chronic stages with less acute alteration of any kind or localisation). The reason why in the later acute stages tubular damage may be expected to become more prominent will soon become clear.

Obviously, endoglomerular changes, if of sufficient intensity, will not long stand alone. The closely related covering epithelium will soon be attacked by the concentrated toxin. And this, we find, is actually the next phase. Epiglomerular changes follow the endoglomerular.

As both elements of the filter (endothelial and epithelial) are now damaged, it becomes abnormally permeable, and the first indication of this is given by the presence of albumen in the capsular spaces, and in the urine if any is passed.

If an animal survives this phase, the conditions must now be modified; for the filter, now colloid-permeable, lets the toxin through, perhaps not so readily as it does crystalloids, but still to some extent. Hence the severer tubular lesions of the later stages result. The tubules are no longer exposed to merely the same concentration of toxin as are other cells of the body; they are, as in chemical nephritis, exposed to a raised concentration by the concentration of the poisonous filtrate by reabsorption.

One advantage of this view, when we come to apply it to human nephritis, is that it is not contradicted by the mere finding in a mainly "tubular" nephritis of less glomerular change than in a glomerular one. It is tr ue that we are regarding tubular alterations, when not merely in proportion to toxic changes in other specialised body cells, as a later development of a condition of uniformly glomerular onset. Nevertheless, the mechanism described is not such as implies progression of the glomerular changes, and merely addition of tubular ones to these at a later stage. Just in so far as the glomerulus becomes toxin-permeable, and the tubules become specially damaged, the glomerulus

becomes the site of a concentration of the toxin diminished in precisely equivalent degree. A completely toxin-permeable glomerulus would not be the site of any concentration of the toxin at all, and it would therefore be that tubular changes sometimes come completely to overshadow the glomerular. One would never, on this theory, expect to find healthy glomeruli in acute nephritis - but it is doubtful if one ever does.

What confirmation of our view can we seek by other experiments? We must expect to find that such changes as other bacterial products produce are similar in incidence. If they are capable only of producing minimal renal changes, we must expect these to be endoglomerular.

For the moment, dealing as we are with toxin experiments, we are omitting consideration of the bacterial element, although we regard it as present in human cases. Its tendencies, however, are to accentuate the incidence described, for the glomeruli form the natural trap in which the bacteria are lysed, and in which a concentration of endotoxin also is therefore produced. The activity of this factor might also conceivably diminish after the onset, for a nephritis may show a bacteriaemia only at the start.

Clinical Features Noted in the Rabbits.

The very early death in rabbits 2,4 and 5 renders estimate of the clinical changes after injection very difficult.

Rabbits 4 and 5 apparently had complete anuria after the injection. It is probable by analogy that the small amount of urine found post-mortem in the case of rabbit 2 was secreted before the injection, and that anuria was really present here also. Similarly, the small amount of urine found post-mortem in the case of rabbit 3 was secreted before the second and fatal injection. In this way one can understand why the urine r eferred to from rabbit 2 was normal, whereas that of rabbit 3 contained albumen - due to the earlier injection.

The acute endoglomerular changes are the cause through stasis, of this anuria, and similar changes are probably the cause of the anuric or oliguric

phase of human acute nephritis. The changes are severe enough to cause a temporary stasis and so suspend filtration.

There is every reason to believe from the histological picture in these rabbits' kidneys that, had they lived, the return of filtration through their glomeruli would have been accompanied by severe albuminuria.

The condition produced is apparently all that is required to explain two of the chief signs at the onset of acute nephritis (anuria or oliguria; albuminuria). Haematuria, from congested inflamed tufts, requires no special study.

For these cases in which oedema is a very early symptom, we can offer no explanation from the kidney changes. We do not think any view of nephritis could do so. Albuminuria, salt retention etc. would all seem to require to act for a certain time, to reach a certain degree, before they can lead to oedema. For oedema as an initial symptom, we must perforce inculpate some extra-renal cause, such as toxic damage to the capillaries generally.

Special Features of Nephritis in Animals due to Streptococcal Toxin.

We see little of interest in a special study of these, but must emphasise the lack of prominent cellular infiltration of the tufts,- associated with the absence of bacteria.

The stages by which the endothelial changes in the glomeruli progressed towards necrosis were by chromatolysis and by nuclear swelling, rather than by karyorrhexis and pyknosis. This affords a strong contrast to the changes produced by diphtheria toxin, as we shall see later. The point is not, however, of great importance.

Experimental Scarlatinal Nephritis compared with Scarlatinal Nephritis in Man.

We cannot strictly compare this experimental nephritis with that in scarlet fever in man more than with any other acute nephritis for we do not believe that the acute nephritis of scarlet fever is invariably of one type. This seems to be the one clear point that emerges from the wealth of contradictory detail in the literature dealing with this disease.

Teissier and Duvoir (160) mention Virchow and Lancereaux as having thought scarlatinal nephritis typically tubular, Kelsch as having described it as glomerular, Frerich, Charcot and Klebs as interstitial, Cornil and Brault and Litten as diffuse.

In this way scarlatinal nephritis seems merely to be a reflection on a small scale of the varying possible incidences which are described in acute nephritis in general.

We are ourselves inclined to believe that the fundamental type is glomerular, and that "tubular" cases are cases observed at a later stage; but we believe this to be true of all cases of acute nephritis, scarlatinal or not, which are glomerular or tubular in post-mortem appearance, or a mixture of these. The special place of interstitial nephritis can hardly be described as simply a stage in the sequence which we believe includes all glomerular and tubular cases, but interstitial nephritis is no more peculiar to scarlet fever than any other type of nephritis is.

When it (interstitial nephritis) occurs in scarlet fever. it may be regarded (Kinloch 76) as representing a type of disease nearer to a nephritic suppuration than the ordinary case of acute nephritis. Kinloch states that it occurs about the sixth day, and usually in the presence of septic complications. This may be the clue to interstitial nephritis not only in scarlet fever but in other infections as well. The appearances present suggest an interstitial inflammation bordering on suppuration, and we suggest that it probably represents a border line form of nephritis in which there is probably some multiplication of organisms within the kidney. On that view, it forms a connecting link with suppurative nephritis and particularly with the "acute infectious nephritis" of Campbell and Rhea before referred to (p. 63.).

A single unconfirmed experiment may be mentioned here. The protocol is not given, for the investigation is recognised as inadequate. One rabbit was given two small injections of No. 3 toxin (.2 c.c. each) at 3 day intervals. Three weeks later, it was given 2 c.c. of No. 3 toxin and died in 4 hours. The changes were not severer than, or different from, those in the rabbits already described.

The experiment had been intended to invoke an anaphylactic factor, analogous to that probably existing in human scarlatinal nephritis, but it failed in this. The problem is complicated by the fact that apparently what would be required is a <u>local</u> (renal), rather than a general, anaphylaxis.

Attempts to produce Chronic Nephritis Experimentally by the use of Streptococcus Scarlatinae along with its Exotoxin.

Only 2 rabbits were used.

Unfortunately, a year had elapsed between these and the original experiments with the toxin, and in that year, for some reason, the virulence and toxin-producing power of the streptococci had greatly diminished. This was no drawback for the chronic experiments now detailed, but it made acute experiments with the streptococcus and its toxin difficult or impossible.

A 1% defibrinated human blood broth was used, and the organisms were incubated in this for 5 days. The broth itself (referred to as Scarl. Strep. Broth A) was used for injections and contained feebly growing streptococci and a little exotoxin.

N.B. The daily doses indicated in the protocols were divided into equal portions and each portion was given at hourly intervals during the day.

Rabbit X.

Healthy rabbit. Weight 900 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

6/10/26. 5 c.c. Scarl. Strep. Broth A intraperitoneally.

7/10/26. Urine 45 c.c. nil abnormal chemically or micro.
9 c.c. Scarl.Strep. Broth A intraperitoneally.

8/10/26. Urine 50 c.c. nil abnormal chemically or micro.
9 c.c. Scarl.Strep. Broth A intraperitoneally.

9/10/26. Urine 40 c.c. nil abnormal chemically or micro.
17 c.c. Scarl.Strep. Broth A intraperitoneally.

11/10/26 Urine (2 days) 40 c.c. nil abnormal chemically or microscopically.
20 c.c. Scarl. Strep.Broth A intraperitoneally.

12/10/26 Urine 20 c.c. nil abnormal chemically.
Micro:- A small number of epithelial cells, no casts.
28 c.c. Scarl.Strep. Broth A intraperitoneally.

13/10/26.Urine 40 c.c. nil abnormal chemically or micro.
26 c.c. Scarl. Strep.Broth A intraperitoneally.

14/10/26.Urine 30 c.c. nil abnormal chemically or micro.
30 c.c. Scarl.Strep.Broth A intraperitoneally.

15/10/26.Urine 60 c.c. Albumen strong positive to boiling and nitric acid tests.
Micro:- A few epithelial cells, a fair number of hyaline casts.
30 c.c. Scarl.Strep.Broth A intraperitoneally.

16/10/26.Urine 10 c.c. Albumen positive to boiling and nitric acid tests. Micro:- A few epithelial cells and some granular casts.
35 c.c. Scarl.Strep.Broth A intraperitoneally.

18/10/26.Urine (2 days) 45 c.c. Albumen strongly positive to nitric acid and boiling tests.
Micro:- A few cells and some granular casts.
40 c.c. Scarl.Strep.Broth A intraperitoneally.

19/10/26.Urine 40 c.c. Albumen positive to nitric acid and boiling tests (Esbach 1/2 gram per litre).
Micro:- A few epithelial cells, a fair number of granular casts.
Died at 10.45 a.m.

P.M.

Localised peritonitis in upper abdomen.

The kidneys were oedematous and pale: their surface was smooth. On the cut surface the cortex was yellowish and pale and the medulla was pale and oedematous.

The liver and spleen were congested.

Right Kidney. 6·3 grams. Left Kidney 5·7 grams.

Kidneys. $\frac{12}{900}$ = ·013.
Body Wt.

MICROSCOPIC EXAMINATION.

Liver and Spleen.

Congestion.

Kidneys.

The glomeruli showed only slight congestion. Many of them showed a greater degree of round celled infiltration than has been noted in any rabbits yet recorded. Some of the endothelial nuclei were pyknotic, a few showed karyorrhexis. In the more affected tufts, there was added to the cellular infiltration a certain slight degree of thickening of the intercapillary tissues which narrowed some of the capillary loops. The epithelium over the tufts was sometimes atrophic, occasionally absent. There was a considerable round celled and fibroblastic infiltration around the afferent arterioles, and to some extent around larger vessels, and very slightly indeed between individual tubules. A few of the tufts were adherent in part or wholly to the outer aspect of the capsule. Such tufts were very small and cellular and, at the periphery, where they adhered to the capsule, a few fibroblasts were entering their substance.

There was often a little cellular infiltration around Bowman's capsule.

The collecting tubules in cortex and medulla were dilated but appeared to be healthy.

Frequently they contained casts.

The convoluted tubules and broad part of the ascending limb of the loop of Henle were in some places apparently healthy, but elsewhere there was fairly extensive swelling of the cells, sometimes with breaking up of the tips into the lumen. Occasionally, the epithelial nuclei were pyknotic and at other times they showed rather faintly or were absent. Quite a few of the tubules showed in the lumen little globules of albumen, evidently derived from the breakdown of the tips of the lining epithelium. In other cases degenerating catarrhal cells were wholly separated from the basement membrane.

RABBIT 12.

Healthy Baby Rabbit. Weight 490 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

12/10/26. 6 c.c. Scarl Strep. Broth A intraperitoneally.

13/10/26 to 22/10/26. Urine: nil abnormal chemically or micro.

22/10/26. 9 c.c. Scarl. Strep. Broth A intraperitoneally.

23/10/26. Urine 15 c.c. Nil abnormal chemically. Micro:- one hyaline cast.
8 c.c. Scarl. Strep. Broth A intraperitoneally.

25/10/26. Urine (2 days) 10 c.c. Albumen trace to boiling and nitric acid tests.
Micro:- some epithelial cells and granular casts.
20 c.c. Scarl. Strep. Broth A intraperitoneally.

27/10/26. Urine (2days) 12 c.c. Albumen trace to boiling and nitric acid tests.
Micro:- fairly numerous epithelial cells and granular casts.
17 c.c. Scarl Strep. Borth A intraperitoneally.

30/10/26. Urine (3 days) 22 c.c. Albumen trace to boiling and nitric acid tests.
Micro:- no cells, a few granular casts.
24 c.c. Scarl. Strep. Broth A intraperitoneally.

2/11/26. Urine (3 days) 12 c.c. Albumen negative to boiling and negative ? to nitric acid tests.
Micro:- A few epithelial cells : one granular cast.
32 c.c. Scarl. Strep. Broth A intraperitoneally.

3/11/26. Urine 10 c.c. Albumen trace to boiling and nitric acid tests.
Micro:- A few epithelial cells, no casts.

DEAD this morning.

P.M.

General peritonitis : yesterday's injections not completely absorbed.

Kidneys:-

Rather mottled surfaces but no granularity. Greatly congested : Medulla very oedematous, but surface of cortex rather mottled.

Right Kidney. 2·7 grams. Left Kidney 2·9 grams.

$\frac{\text{Kidneys.}}{\text{Body Wt.}} = \frac{5·6}{490} = .011.$

The liver and spleen were congested.

MICROSCOPIC EXAMINATION.

Kidneys.

The glomeruli showed considerable congestion with great swelling of the endothilium and some round celled infiltration. The covering epithelium was swollen and prominent, often lost. Occasionally a small area in some tufts showed loss of nuclear structure.

In some cases the tufts near the points of entrance of afferent arterioles were overcellular, chiefly as the result of round celled infiltration, but some fibroblasts were present as well. Around the afferent arterioles there was a little cellular infiltration, but none about larger vessels.

In the tubules degeneration was widespread. Many nuclei showed marked pyknosis. Others showed karyolysis or occasionally karyorhexis. There was some catarrh and a good deal of breaking down of the luminal part of the cytoplasm. A number of the tubules were lined by a low cubical epithelium and the lumen of these contained casts. Where no breakdown of the cytoplasm had taken place the cells were greatly swollen and the lumen of the tubule was obliterated : in other places where the cytoplasm had disappeared an irregular arrangement of pyknotic nuclei represented the tubule.

There was no increase of connective tissue.

There were peculiar foci in the boundary zone occupied by homogeneous albumenous material with a few scattered nuclei and perhaps one or two R.B.C. They seemed to represent the complete necrosis of one or two adjacent sections of tubule.

No fat was found in the organ.

SUMMARY.

These two rabbits show much the same results, save that in the latter, probably because of higher dosage, there are more severe acute changes.

Both show quite clearly the later spread of severe damage from glomeruli to tubules already noted and discussed.

Both show a greater cellularity of the tufts than previous experiments. The greater part of this is probably due to the use of bacteria with the toxins and not to chronicity.

There are, however, a rather increased number of fibroblastic nuclei in the glomerular tufts and there is a slight thickening of and infiltration around the afferent arterioles. These are the only indications of commencing progressive nephritis. They are exceedingly slight and they give no encouragement to proceed along these lines to attempt the production of a granular or contracted kidney.

It is possible to regard them, however, as indicative of the site of the earliest changes in progressive nephritis (chronic interstitial nephritis) in man.

We do not wish in any way to emphasise these changes, for admittedly they are far too slight to attach much significance to. The number of experiments is also far to small, and their duration insufficient.

Though the chronic changes are very slight, it may be noted that they do start in the glomeruli, and are not focal. In neither of these respects do they resemble spontaneous nephritis.

EXPERIMENTS WITH DIPHTHERIA TOXIN.

Animals used. Rabbits. A,G,H,J,K,L,M,N,O,R,T.
Rats. 10 and 13.

The toxin used was obtained from the Wellcome Physiological Research Laboratories. It contained no preservative, and its strength was 10 units per c.c. It was suitably diluted for the various doses given. Diluted toxin was made in small quantities only and was not kept for long (not over 2 days) before use.

Rabbit A.

Healthy rabbit. Weight 1530 grams.
Urine before injection (3 examinations) Nil abnormal on chemical or microscopic examination.

11/3/26. 2 p.m. 1 c.c. diluted D.T. subcut. (=.4 unit.)

12/3/26. Total urine 55 c.c. Very turbid and mixed with faeces as the animal has had diarrhoea. Albumen, a trace to boiling and nitric acid tests. Micro:- Much contaminating material: one leucocyte, one R.B.C., one hyaline cast.
10 a.m. Died.

P.M.
Congestion of all organs; otherwise nil abnormal naked eye.
Spleen:- .56 gram.

Right kidney 6.37 grams. Left kidney 6.27 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{12.64}{1530} = .008$

Microscopic Examination.

Spleen:-
Congested.
Liver:-
Congested. Fat in some cells.
Kidneys:-
A fair amount of fat was present in the tubules of the cortex, and to a lesser extent in those of the medulla. The basal part of the cell was chiefly affected, but all portions were involved. The fat was in the form of a very fine dusting. The nuclei of the cells were for the most part clearly seen, though a few, where the fat was most marked, were obscured.
There was a very small amount of fat in some of the endothelial nuclei, which were also pale. The basement membrane of some of the capillaries was distinctly swollen, thus separating them unduly from one another. The capillaries themselves were greatly dilated, and filled with R.B.C. or occasionally with thrombus. Occasionally there was an appearance suggesting the rupture of one capillary into another, and occasionally a loop was faintly staining, showing no nuclei and was apparently necrotic. There was infiltration of the majority of the tufts by polymorphs, which were often degenerating; there were also apparently a few infiltrating small round cells. A few of the endothelial nuclei showed some karyorrhexis. The epithelium covering the tuft was swollen and very prominent. For the most part it was in situ, but occasionally it was absent over a necrotic part of the tuft. Both types of

tuft showed some albuminous material in the capsular space, and sometimes this brought about adhesion of the tuft to the capsule. The parietal epithelium was oftenswollen and prominent as well.

The basement membrane of Bowman's capsule was swollen and prominent, and often separated by oedema from the surrounding tubules, or occasionally by a ring of small round cells.

There was slight round celled infiltration round some afferent arterioles and occasionally between tubules.

All vessels, both of cortex and medulla, were greatly congested.

Only one or two casts were noted (in first convoluted tubules).

The convoluted tubules showed moderate cloudy swelling, with sometimes disintegration of the tips of the cells. Al most,all the nuclei stained well, however, and there was no catarrh.

Summary.

Endoglomerular,with,in some cases, also epiglomerular changes. Slight tubular changes.

RABBIT G.

Healthy Rabbit. Wight 1780 grams.
Urine before injections (3 examinations) nil abnormal chemically or microsoopically.

28/5/26. 3 p.m. 5 c.c.water containing ·1 unit D.T. intraperitoneally.

29/5/26.) Urine nil abnormal chemically or
31/5/26.) micro.

31/5/26. 9 a.m. 3½ c.c. water containing ·15 unit D.T. intraperitoneally.

1/6/26. Urine nil abnormal chemically or micro.
9 a.m. 4 c.c. water containing ·3 unit D.T. intraperitoneally.

2/6/26. Urine nil abnormal chemically or micro.
9 a.m. 9 c.c. water containing .9 unit D.T. intraperitoneally.

3/6/26. Rabbit found dead but warm in the morning.

P.M.

The kidneys were slightly enlarged. They showed a smooth, congested surface. The cut surface of the cortex showed some opacity with very prominent congested glomeruli, and what appeared to be a number of small haemorrhages.

The medulla was congested and oedematous.

The liver and spleen.were congested, and the latter was rather soft. Otherwise nothing abnormal was noted naked eye.

Right Kidney. 8·1 grams. Left Kidney 8·35 grams.

Kidneys / Body Wt. = 16·45 / 1780 = .009 Spleen ·73 grams.

P.M. Urine about 1 c.c. from bladder. Albumen was present in considerable quantity to the nitric acid test. Micro:- No casts, but renal and bladder epithelial cells in fair numbers.

MICROSCOPIC EXAMINATION.

Spleen:-

Congested.

Liver:-

Congested with some fatty change at the periphery of the lobules.

Kidneys:-

The glomeruli were exceedingly congested and were distended so as usually almost to fill the capsular spaces. Every capillary loop was greatly distended with red blood capsules.

The endothelial cells of the tuft showed very marked degeneration..Many of them showed advanced karyorrhexis and their nuclei were represented only by a few grains of chromatin dust. Others were pyknotic, while in still other parts the nuclei were completely gone. Scarcely a single normal endothelial cell was seen anywhere. There were a few, generally degenerating, polymorphs obvious in the tufts, but there was also a suspicion that many of the breaking up nuclei might be polymorphis and not enthothelial. The total number of visible nuclei in the tuft was not increased.

The epithelium covering the tuft was not complete, and its nuclei, where they were present, were often pyknotic.

Upon the whole, the worse the endoglomerular changes, the more change there was in the covering epithelium.

In the more affected tufts, there was some albuminous material in the narrow capsular spaces, and occasionally even a few red blood capsules.

The epithelium of the parietal aspect of Bowman's capsule was little affected but was beginning to get ragged.

Some glomeruli were almost completely disintegrated. Others showed pretty extensive necrotic portions.

The intertubular plexus was intensely congested as were all the vessels of the kidney; the nuclei of the endothelial cells of the intertubular plexus were very pyknotic and in some places the

blood seemed to lie on both sides of the endothelial lining, as if it had been detached from its base-ment membrane.

There was no evident cellular infiltration or oedema of the interstitial tissue.

There were apparently small haemorrhages here and there between convoluted tubules.

The cells of the convoluted tubules showed advanced degeneration. Many, even the majority, of the nuclei were markedly pyknotic. Others showed karyorrhexis, whilst yet others were faintly staining. The cytoplasm showed sometimes loss of the tips of the cells, sometimes vacuolation. There were many catarrhal cells, and sometimes the whole epithelium had become detached and la y free or had disappeared.

There were a few casts present.

The broad part of the ascending limb of the loop of Henle presented much the same appearances as the convoluted tubules. The collecting tubules etc. were normal, save for the occasional presence in the lumen of some pyknotic epithelial cells derived from higher up.

There was slight fatty change in the form of sparse minute globules in the cells in a fair number of convoluted tubules. There was fairly widespread but not marked fatty change in many of the tubules in the medulla (cheifly, but entirely, the ascending limb of Henle's loop in the boundary zone).

Summary.

Marked glomerular changes, endo- and epi-glomerular, leading to glomerular hyper-permeability. Fairly marked tubular changes also, as might have been expected because of the repeated injections.

Microphotograph. 8.

Rabbit H.

Healthy rabbit. Weight 1000 grams.
Urine before injections (6 examinations) nil abnormal chemically or microscopically.

14/6/26. Intraperitoneal injection of 500 c.c. of slightly hypertonic saline containing .1 unit D.T.

15/6/26. Urine 300 c.c. Albumen negative to nitric acid and boiling tests. Micro:- One hyaline cast, two leucocytes, one R.B.C.
Intraperitoneal injection of 500 c.c. of slightly hypertonic saline containing .1 unit D.T.

16/6/26. Urine 400 c.c. Nil abnormal chemically or microscopically.
Intraperitoneal injection of similar fluid commenced, but during injection animal died suddenly.

P.M.
200 c.c. of fluid found in peritoneal cavity.
Kidneys rather congested.
Nil abnormal other organs naked eye.

Right Kidney 4.01 grams. Left Kidney 4.01gms.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{8.02}{1000} = .008.$

Spleen .41 gram.

Microscopic Examination:-

Liver and Spleen:-
Nil to note.

Kidneys:-
The glomeruli were not congested and were small. The endothelial nuclei were rather swollen, as were the basement membranes of the capillary walls. There were small numbers of infiltrating small round cells and polymorphs. A few of the endothelial nuclei showed some karyorrhexis.

The epithelium covering the tufts was intact and there was nil abnormal to note in the glomerular spaces.

The endothelium of the intertubular plexus was darkly staining and prominent, and formed a prominent feature in the microscopic field.

The vessels of the cortex and medulla were rather congested.

There was hardly any catarrh of the tubules, but the tips of the cells of the convoluted tubules and of the broad part of the ascending limb of the loop of Henle had largely broken down or were vacuolated and breaking down. The nuclei, however, stained well. No fat was visible anywhere.

Summary.

The changes are mild. They are chiefly glomerular but are present in the tubules also. Death seems to have been due more to the bulk of the fluid injected than to its toxicity. It is possible that the enormous diuresis quite early swept some of the toxic molecules into the filtrate, and that this accounts for the early signs of damage in the luminal edges of many epithelial cells of the tubules.

Rabbit K.

Healthy rabbit. Weight 750 grams.
Urine before injections (3 examinations) nil abnormal chemically or microscopically.

21/6/26. 1/80th gram Pot.Bichrom. in 10 c.c. of water intraperitoneally.

22/6/26. Urine nil abnormal chemically or microscopically.
1 p.m. 1/60th gram Pot.Bichrom. in 10 c.c. of water intraperitoneally.

23/6/26. Urine, albumen positive to boiling and nitric acid tests. Micro:- A few leucocytes, no casts.
3 p.m. .025 unit D.T. subcutaneously.

5 p.m. .025 unit D.T. subcutaneously.

24/6/26. Urine 8 c.c. (previously had varied from 20 to 50 c.c.) Albumen positive to boiling and nitric acid tests (fair amount). Micro:- A few leucocytes, many epithelial cells and a great number of R.B.C., no casts.
10 a.m. .01 unit D.T. subcutaneously.

1 p.m. .01 unit D.T. subcutaneously.

25/6/26. Urine 2 c.c. Albumen positive to boiling and nitric acid tests. Micro:- very numerous epithelial cells; one or two small hyaline, partly epithelial, casts: one or two R.B.C.

26/6/26. Urine - none.
Rabbit dead but warm this morning.

P.M.

The liver appeared congested and fatty, the spleen congested, and the kidneys congested with some opacity of the cortex.

Right kidney 3.4 grams. Left Kidney 3.25 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{6.75}{750} = .009.$

Spleen .4 gram.

Microscopic Examination:-

Liver and Spleen:-
Congested; no furtherchange noted.

Kidneys:-

There was moderate congestion throughout the whole organ.

The evidence of tubular change due to the chrome poisoning (see series Chrome p.116 etc.) was unexpectedly slight. There was catarrh here and there, but it was only slight, and the nuclei of the epithelium generally stained well, though a minority were rather faint. Here and there among the convoluted tubules a degenerated tubule could be seen showing only one or two faintly staining nuclei. The generality of the tubules showed a rather low type of epithelium and rather unusually dark eosinophil staining of the cytoplasm (compared with other epithelial areas in the section). A few casts were present in the lumen of convoluted tubules.

The glomeruli showed swelling of the endothelial cells and of their nuclei. There were a few infiltrating cells. Some were polymorphs. Others varied from a round celled appearance, to definite connective tissue cells. The more definite connective tissue cells were near the point of entrance of the afferent arterioles. There was occlusion, mainly from endothelial swelling, of many glomerular capillaries.

There was some karyorrhexis in some of the tuft endothelial cells.

The epithelium of the tuft was swollen, and sometimes one of its cells lay free in the capsular space. Though mostly present, in a number of tufts it was practically gone over projecting congested capillaries. The parietal epithelium was normal or a little swollen.

Occasionally there was a little albuminous material in the capsular spaces. Some slight round celled infiltration was seen occasionally between cortical tubules, and there was distinct round celled infiltration round some of the smaller vessels, especially some of the afferent arterioles, and also round some of the glomeruli. There was some hyaline swelling of the wall of a few afferent arterioles.

Fat:- There was a fine and very slight dusting of the extreme bases of cells of many of the convoluted tubules. A much more distinct fatty change was seen in many of the collecting tubules in the medulla.

There was no fat visible in the glomeruli.

Summary.

Glomerular changes of the type found in other diphtheria toxin experiments, and tubular changes of the type found in chrome experiments are both seen here,

without any evidence that the one augmented the other. There was nothing to encourage further work with a combination of crystalloid and colloid poisons. The slight connective tissue increase in the tufts was not sufficient to draw any conclusions from.

Rabbit J.

Healthy rabbit. Weight 830 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

21/6/26. 10 a.m. .025 unit D.T. subcutaneously.

11 a.m. .03 " " "

12 a.m. .025 " " "

1 p.m. .025 " " "

2 p.m. .05 " " "

4 p.m. .025 " " "

22/6/26. Urine 30 c.c. nil abnormal chemically or microscopically.
9 a.m. .03 unit D.T. subcutaneously.

11 a.m. .025 " " "

12 a.m. .025 " " "

23/6/26. Urine 10 c.c. Albumen positive to boiling test, doubtful to nitric acid test.
Micro:- Very numerous epithelial cells, one or two hyaline and granular casts.
Found dead this morning.

P.M.
Slight peritoneal effusion.

Liver, Spleen and Kidneys congested; parasites in liver.

Right Kidney 3.6 grams. Left Kidney 3.4 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{7}{830} = .008.$

Spleen .6 gram.

Microscopic Examination:-

Spleen and Liver:-
Congested, no fatty change in liver.

Kidneys:-
The glomeruli showed marked hyaline swelling of the endothelial cells and occlusion thereby of most of the capillaries of the more affected tufts. Many of the endothelial nuclei were swollen and pale; many others showed pyknosis, with or without varying degrees of karyorrhexis. There was very little cellular infiltration of the tufts, but some showed the presence of a few small round cells.

The epithelium covering the more affected tufts (and these were in the majority) was swollen, rarely locally desquamated. Proliferation of the epithelium was occasionally apparent, with possible early crescent formation.

A minority of glomeruli were small and congested without marked endothelial swelling and these showed complete unswollen capsular epithelium.

The intertubular plexus of the cortex was markedly congested.

The tubules showed relatively little change. Most of the nuclei showed up well, but here and there there was partial karyolysis or some pyknosis. One or two catarrhal cells were noted, and one or two casts.

The medulla was congested.

No fat was found anywhere.

Summary.

In fine, though tubular and glomerular changes are both evident, the glomerular are the more marked and the more widespread. The changes are again interpretable as primarily endoglomerular, with subsequent alterations in the covering epithelium. There is no evidence that repeated small doses modify an acute experiment, unless

we attribute the minor proliferative changes seen occasionally in the epithelium covering the tufts to this modification of the method.

Rabbit L.

Healthy rabbit. Weight 870 grams.
Urine before injections (4 examinations) Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.

23/6/26. 9.45 a.m. .025 unit D.T. subcutaneously.

3.45 p.m. .025 " " "

5 p.m. .025 " " "

24/6/26. Urine 25 c.c. Albumen doubtful to boiling test; distinct trace to nitric acid test.
Micro:- Crystals, a few epithelial cells, numerous R.B.C., no casts.

10.15 a.m. .01 unit D.T. subcutaneously.

12.45 p.m. .01 " " "

25/6/26. Urine - none.

26/6/26. Urine - none.
Rabbit found dead but warm.

P.M.

The right kidney was considerably emlarged: the pelvis of the ureter was distended with blood. The cortex was broadened and showed some very fine yellow mottling. The cortex and medulla were both deeply congested. There was a particularly marked congestion in fan-shaped areas in the boundary zone.

The mucous membrane of the pelvis of the ureter was congested and haemorrhagic and the greater part at least of the blood clot mentioned must have come from there.

The Left Kidney was not distinctly enlarged. The cortex and medulla showed congestion as before, but without the peculiar "fan" shaped areas in the boundary zone. There was the same fine yellow mottling of the cortex without, however, distinct broadening.

Liver congested.

Spleen, somewhat congested: fleshy.

Nothing abnormal was noted in the other organs naked eye.

Microscopic appearances:-

Spleen:-

Great congestion of the pulp, which was packed with red blood corpuscles but also contained an increased number of lymphocyte like cells. The endothelial cells lining the sinusoids were swollen and prominent, in some cases detached. The basement membrane lining the sinusoids was also swollen. A few small haemorrhages were seen here and there.

There was considerable congestion of the Malpighian bodies, with apparently destruction of a number of their constituent lymphoid cells.

Liver:-

Showed marked congestion and a little cloudy changes, with some fatty changes at the periphery of the lobules.

Kidneys:-

The glomeruli were congested but many of the capillaries of the tufts were occluded by swelling of the endothelial cytoplasm, or by thrombosis. In many, it was difficult to ascertain the original cause of the occlusion, for all structure was lost in parts of most of the tufts and replaced by a faintly eosinophil, finely granular, but almost hyaline material. Such endothelial nuclei as persisted were either pyknotic or showed advanced karyorrhexis. A very few infiltrating small round cells were seen (no more than in controls) and these were apparently in the lumen of partially occluded capillaries. Often the interior of the tuft was structureless in its greater part, but showed perhaps one very distended patent loop full of R.B.C., and in another corner a group of cells, apparently endothelials, undergoing karyorrhexis. The epithelium covering the tuft was swollen and therefore prominent. It had seldom actually disappeared, so that its covering line of nuclei showed up in marked contrast to the almost structureless tuft within. The capsular spaces contained albuminous material in many instances, and here and there the tufts were gummed to the parietal aspect of the space, and the covering epithelium of the tuft was flattened.

The tubules showed pretty advanced changes also. There were numerous pyknotic nuclei in their epithelium. There was marked catarrh, with complete necrosis and loss of nuclear stain in many of the catarrhal cells. Elsewhere, some tubules (convoluted) were lined by low

cubical or even flattened cells. Most of the portions of the first convoluted tubule leaving the glomerular capsule, and a great many of the descending and ascending limbs of the loops of Henle, and the collecting tubules both in cortex and medulla contained hyaline casts, apparently of the same nature as the albuminous material in the capsular spaces. The lumen of a number of the tubules also contained some chromatin dust, apparently derived from the nuclei of epithelial cells.

The cells lining the collecting tubules appeared healthy, but the cells of all the "active" parts of the tubules showed the changes described.

There was no perceptible infiltration in the connective tissue of the organ.

Fat:- There was a minimal amount of fatty dusting of the very bases of the cells of some of the broad parts of the ascending limbs of the loops of Henle. No fat was found in any other part of the organ.

Summary.

The incidence of alterations in this kidney also is predominantly glomerular and the more advanced alterations are in the endothelials within the tufts. The dosage has evidently been very high for this rabbit and the accompanying tubular changes are probably better interpreted as being a result of the severity of the general toxic action than in terms of a secondary damage due to alterations in the glomeruli.

The entire lack of urine in the last two days evidently indicates glomerular stasis and suspension of filtration.

Rabbit M.

Healthy rabbit. Weight 920 grams.
Urine before injections (4 examinations), no albumen to boiling or nitric acid tests. Micro:- Crystals, no cells, no casts.

5/7/26. 10 a.m. .025 unit D.T. subcutaneously.

6/7/26. Urine 20 c.c. Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.

7/7/26. Urine 72 c.c. Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.

9 a.m. .050 unit D.T. subcutaneously.

8/7/26. Urine 85 c.c. Albumen negative to nitric acid and boiling tests.
Micro:- Crystals, no cells, no casts.

3.30 p.m. .001 unit D.T. subcutaneously.

5.15 p.m. .001 " " "

9/7/26. Urine 150 c.c. Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.

10/7/26. Urine, albumen doubtful to both boiling and nitric acid tests.
Found dead but warm this morning.

P.M.

The kidneys were congested, with a possible slight opacity of the cut surface of the cortex. The spleen was soft.

Right Kidney 4.02 grams. Left Kidney 3.9 grams.

$$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{7.92}{920} = .009.$$

Spleen .5 gram.

Microscopic Examination:-

Spleen:-

Congestion of pulp. Swelling and sometimes detachment of endothelial cells lining sinusoids: some fibrinous clots here and there: slight decrease of lymphoid tissue of Malpighian bodies.

Liver:-
Congestion.

Kidneys:-
The glomeruli showed swelling of their basement membranes and of the endothelial cells, with resulting block of many capillaries. Occasionally, other capillary loops were distended.

A few of the endothelial nuclei were swollen, but most were pyknotic, and some were commencing to undergo karyorrhexis. The changes were not so marked as in the kidneys of previous animals treated with diphtheria toxin (a point which may be correlated with the very evident lack of diminution in the quantity of urine in the present case).

The tufts showed, however, in addition, a small number of infiltrating small round cells. These were not necessarily significant being found in some controls, but here they were arranged especially near the point of entrance of the afferent arterioles, where also there were some connective tissue cells just entering the tuft.

The epithelium covering the tuft was practically intact and was only in places swollen. There was only occasionally, in one or two places, a very small quantity of albuminous material.

In three or four only of the tufts was seen the "blood-cyst" appearance described by some observers (see literature pp.157-9). The cysts were lined by atrophic endothelium and occupied more than half the tuft. The remaining portion of the tuft was compressed and therefore appeared overcellular. A thinned out but distinct epithelium was stretched out over the bulging part of the cyst where it projected into the capsular space. No R.B.C. or albuminous material were seen in such capsular spaces.

The contents of the cyst were granular material, chiefly thrombus and R.B.C. The convoluted tubules and loops of Henle showed no distinct catarrh but the tips of many cells were breaking down, and the nuclei of a few showed faint staining or did not stain at all.

No casts were visible. The intertubular plexus of the cortex was congested. The medulla was congested but the collecting tubules were healthy.

Fat was present in the bases of cells of most of the broad parts of the loop of Henle. No fat was demonstrable elsewhere in the organ.

Microphotograph. 9.

Summary.

A predominantly endoglomerular change is clearly indicated.

Rabbit N,

Healthy rabbit. Weight 785 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

In this rabbit and in a number of others, various other organisms or toxins were injected subsequently to the diphtheria toxin. The rationale of the procedure was much the same as that indicated for repeated hourly injections. Repeated daily or less frequent injections in animals tend rapidly to produce an immunity with no accompanying renal changes. On the assumption that the two facts are related, we endeavoured by various means to prevent the establishment of immunity and thus hoped to get progressive changes. Dosage as nearly continuous as possible is one of the ways in which this was attempted. Repeated change of the particular organism used was another method tried, and is illustrated here. It was recognised that it would be difficult to assign to any particular poison used its share of the damage, if a progressive change was obtained.

4/7/26. Blood urea 19 mgms. /100 c.c.

7/7/26. 9 a.m. .002 unit D.T. subcutaneously.

8/7/26. Urine 75 c.c. nil abnormal chemically or microscopically.
3 p.m. .001 unit D.T. subcutaneously.

5 p.m. .001 unit D.T. subcutaneously.

9/7/26. Urine 100 c.c. nil abnormal chemically or microscopically.

10/7/26. Urine not collected.
9.30 a.m. .002 unit D.T. subcutaneously.

12/7/26. Urine (2 days) 200 c.c. Albumen doubtful to boiling test, faint trace to nitric acid test.
Micro:- Nil abnormal.
9 a.m. .002 unit D.T. subcutaneously.

1 p.m. .002 " " "

3 p.m. 1/2 c.c. 2 day broth culture of staphylococcus aureus intraperitoneally.

At 4 p.m. the animal appeared to be dying but next day had rallied considerably.

13/7/26. Urine 8 c.c. Albumen a faint haze to boiling test, negative to nitric acid test.
Micro:- A fair number of renal epithelial cells, and a few hyaline casts.

14/7/26. Urine about 60 c.c. Albumen doubtful trace to both boiling and nitric acid tests.
Micro:- One or two renal epithelial cells, no casts.

11 a.m. 1/2 c.c. 2 day broth culture of staphylococcus aureus intraperitoneally.

15/7/26. Urine 55 c.c. Albumen a faint haze to boiling test, negative to nitric acid test.
Micro:- A few epithelial cells, a few hyaline granular and epithelial casts.
11 a.m. 1 c.c. 2 day broth culture of staphylococcus aureus intraperitoneally.

16/7/26. Urine 40 c.c. Albumen negative ? to boiling test, negative to nitric acid test.
Micro:- A few epithelial cells, some hyaline epithelial casts.

4 p.m. 2 c.c. 2 day broth culture of staphylococcus aureus intraperitoneally.

19/7/26. Urine 60 c.c.(3 days) Albumen negative ? to boiling test, negative to nitric acid test.
Micro:- One or two degenerating epithelial cells, no casts.

1 p.m. 1/2 c.c. broth culture of Morgan bacillus No, 1 subcutaneously.

20/7/26. Urine 65 c.c. Albumen negative ? to boiling and nitric acid tests. Micro:- Nil abnormal.

10 a.m. 2 c.c. Morgan No. 1 Broth intraperitoneally.

21/7/26. Urine 42 c.c. Albumen negative ? to boiling test, faint trace ? to nitric acid test.
Micro:- A single epithelial cell, no casts.

10 a.m. 1/2 c.c. 4 day broth culture of haemylotic streptococcus intraperitoneally.

(These were not the haemylotic streptococci already used to produce scarlet fever toxin. The present streptococci turned out to be only slightly toxic - as even this experiment shows).

22/7/26. Urine 80 c.c. Albumen negative to boiling and nitric acid tests.
Micro:- Crystals, no cells, no casts.

12.15 p.m. 25 mgms. /100 c.c(Blood urea.)

12.30 p.m. 2 c.c. Haemolytic Strep. broth intraperitoneally.

23/7/26. Urine 100 c.c. Nil abnormal chemically or microscopically.

1 p.m. 6 c.c. Haemolytic Strep. broth intraperitoneally.

24/7/26. Urine 95 c.c. Albumen negative ? to boiling test, negative to nitric acid test.
Micro:- Nil abnormal.

Blood urea 49 mgms./100 c.c.

11 a.m. 6 c.c. Staphylococcus aureus broth intraperitoneally.

25/7/26. Moribund. Killed 6 p.m.(110 c.c. urine passed in last 36 hours; nil abnormal chemically.)

P.M.

General peritonitis.
Right kidney 5.3 grams. Left kidney 6.9 grams. (a distinct difference)

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{12.2}{785} =$ .015. (Unusually high).

Both kidneys were congested.

Microscopic Examination:-

Spleen:-
Congested.

Liver:-
Congested; cloudy change; fat in cells of periphery of lobules.

Kidneys:-
It was obvious at first glance that it would be difficult to disentangle the effects of the last heavy injection from those of the previous injections, but we will endeavour to distinguish to some extent between the recent and the apparently more chronic alterations.

The glomeruli gave the impression that they had never been allowed to recover completely from acute

changes but that the repeated doses had served to do little more than renew this acute change without any chronic alterations being superadded.

Some glomerular capillary loops were very congested, others were apparently obliterated by hyaline swelling of the basement membrane of the capillaries. Still others showed a narrowed and empty but not obliterated lumen suggesting that the apparently completer block elsewhere in the tufts had prevented access of blood to these narrow but patent loops. The endothelial nuclei in most tufts were probably rather under the average in number, some having apparently been completely destroyed. In some tufts very few nuclei were visible, and the surviving endothelial nuclei were pale and swollen. In most of the tufts there was, however, a sufficient number of inflitrating small round cells (sometimes in, sometimes between, capillaries) to make the tuft as a whole appear normally cellular. In a few, the number of such infiltrating cells were sufficient to make the tuft distinctly overcellular. Overcellularity, when present, was usually most marked near the point of entrance of the afferent arteriole, and it was here that the only possible evidence of commencing chronicity was found, for the round cells at this point were mixed with a small number of fibroblasts. Round celled infiltration was observed around the afferent arteriole as it proceeded to the tuft, again together with a number of fibroblasts. The adventitial tissue of the afferent arterioles and of the larger vessels of the cortex showed a pretty marked oedematous thickening, with, however, relatively few cells. In some cases the media also was thickened and a commencing fibrosis of the media appeared to exist.

Turning to the epithelium covering the tuft, we found it to be in the majority of tufts, normal, but in the less cellular ones, where intraglomerular disintegration, with congestion and loss of endothelial nuclei, was more evident than infiltrative changes, there were by contrast marked epithelial alterations. There was never proliferation of the epithelium, but many of the epithelial cells were completely gone, whilst others were in process of detachment or actually desquamated into the capsular space. It was in the capsular spaces of such tufts that one could make out a few R.B.C. and a little albuminous material.

In most cases the capsular space was small or not evident. The parietal epithelium of the capsule was complete but pyknotic. The basement membrane underlying it was thickened and often separated by a clear oedematous space with a few round cells from the surrounding tubules.

The tubular changes also were marked, but here the recent changes were the less evident of the two There was no catarrh, but in some tubules, chiefly first

convoluted tubules, there was swelling of the cells, with swelling and pallor of their nuclei.

Many other tubules showed marked atrophic change. These appeared to be chiefly loops of Henle and second convoluted tubules. The lumen of each tubule was widened, and t his was due to a great flattening of the lining epithelium, which was sometimes almost endothelial like. The nuclei were round, small, and darkly staining.

There was no cellular infiltration or increase of connective tissue around such tubules.

One or two casts were seen in the portions of first convoluted tubules leaving badly affected glomeruli. Otherwise no casts were seen.

No fat was seen anywhere.

Summary and Discussion.

There is acute glomerular change, endoglomerular and also epiglomerular, with slight evidences of recent degenerative change in the tubular epithelium. At the same time, there is an atrophic lining to many secreting tubules, apparently a residue of previous acute damage. Such atrophied tubules are mainly second convoluted tubules.

Such signs of chronicity as are evident are in the vascular apparatus and are concentrated chiefly on the point of entrance of the afferent arterioles into the tufts. They consist of a narrowing of the lumen of such arterioles and a very moderate fibroblastic and round celled proliferation around them.

There is a suggestion of commencing arterio-sclerotic change in the larger vessels of the cortex.

One would gather that at the present stage a small degree of permanent glomerular damage is inevitable,

but that it would be small, and quite inadequate to lead to symptoms of renal insufficiency.

The changes in afferent and other arterioles may be entirely due to the injections directly, but we have to bear in mind that from the beginning of the experiment most of these vessels have had to overcome a greatly increased resistance in the glomerular capillary bed, and this may have contributed to the changes. The experiment seems to agree in any case with the suggestion of Klotz (79) that arterio-sclerotic changes in the smaller vessels of the kidney are more likely to be a part of the changes induced in nephritis than an independent arterio-sclerosis causing a change simulating nephritis.

As to the tubular changes, we regard the recent cell swelling etc. as due to the action of the last dose. It conforms to our previous experience that this change should be slight, and less that the acute glomerular change present. The selectivity for the first convoluted tubules here is natural enough, for the toxin in the plasma has not at that portion of the tubule been much rediluted by reabsorption from the filtrate.

The atrophic changes, on the other hand, we regard as a repair of extensive damage to convoluted tubules (chiefly second). Such extensive destruction is, though early, not an initial result of the first injections (i.e. it ~~comes~~ came after the tufts have become

toxin-permeable). The lack of greatly raised blood urea three days before death we attribute to the lack of acute changes in most of the tubular cells at that stage. The rise in blood urea after the next, the second last, injection probably indicates that that injection renewed and accentuated the acute glomerular changes, leading to stasis. Probably, too, it caused the acute catarrhal changes noted in the first convoluted tubules, and these also would tend to raise the blood urea. Atrophic cells are perhaps unlikely to reabsorb an adequate amount of fluid, but they are unlikely to allow of a mechanical "seeping back" of urea etc. Probably it was only these atrophic changes that were present before the earlier of these two blood urea estimations.

Finally, the experiment practically failed in its initial object of producing distinct chronic renal changes analogous to those in man. Very slight alterations, which may have been the heralds of such changes, were however noted.

Rabbit O.

Healthy rabbit. Weight 1400 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.
Blood Urea 20 mgms. /100 c.c.

12/7/26. 4 p.m. .06 unit D.T. subcutaneously,

13/7/26. Urine 150 c.c. nil abnormal chemically or microscopically.

12 a.m. .05 unit D.T. subcutaneously.

Starved all day.

2 p.m. Blood Urea 70 mgms./100 c.c.

3 p.m. killed.

P.M.

A small amount of urine was obtained from the bladder. It showed no albumen to nitric acid test. Microscopically, there were one or two hyaline casts, and some renal and bladder epithelial cells.

No naked eye changes in the organs.

Right Kidney 3.85 grams. Left Kidney 3.85 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{7.7}{1400} = .006.$

Spleen .65 gram.

Microscopic Examination:-

Liver:-
Congested.

Spleen:-
Pulp congested, and contained an unusual number of lymphocytes. Prominence of epithelials lining sinuses.

Kidneys:-
The nuclei of the glomerular endothelial cells were rather pale, and the tufts contained a small number of infiltrating small round cells (not decidedly greater than in some controls, however). Some of the endothelial nuclei were showing chromatolysis. The basement membranes of the capillary loops were thickened and hyaline, and many capillaries had their lumen narrowed in this way. The hyaline material did not appear to be thrombus, although there was in addition

a little thrombus in some loops. Occasionally a tuft, especially in its superficial parts, showed greatly congested distended loops but there was not much blood in the majority of the tufts. The epithelium covering the tuft was for the most part intact but was detached over a few of the more severely affected loops.

There was no distinct alteration in the tubules and nothing abnormal in the interstitial tissue or in the vessels beyond a little hyaline thickening of the intima of afferent arterioles.

No fat was found anywhere.

Summary.

Glomerular changes, almost confined to the endothelium.

Rabbit R.

Healthy rabbit. Weight 950 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

22/7/26. At intervals between 12 a.m. and 4 p.m. was given a total of 300 c.c. of saline containing .15 unit D.T. intraperitoneally.

23/7/26. Between 12 a.m. and 4 p,m. given 150 c.c. of saline containing .10 unit D.T. intraperitoneally. (In the morning the fluid of the previous day had not been completely absorbed).

24/7/26. Not touched. Urine very dilute and nil abnormal found.

25/7/26. Dead. 100 c.c. of fluid still in peritoneal cavity so that the total of diphtheria toxin absorbed cannot have been over .20 unit.

P.M.

Right Kidney 3.9 grams. Left Kidney 3.4 grams.

$$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{7.3}{950} = .008$$

Spleen .75 gram.

Nil abnormal naked eye in the organs.

Microscopic Examination.-

Liver:-
Nil abnormal.

Spleen:-
Congestion of pulp; endothelials prominent.

Kidneys:-
The glomeruli were congested. There was possible slight swelling of the basement membrane of capillaries and slight round celled infiltration in the tufts but, bar the glomerular congestion, no change was noted in either glomeruli or tubules which was definitely outside the range of appearances in controls.
Some of the tubules were dilated, a finding which can readily be correlated with the diuresis present.
No fat was found anywhere.

Rat 10.

Healthy white rat. Weight 90.5 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

10/3/26. 1 p.m. 1/2 c.c. diluted D.T. subcutaneously. (.2 unit).

11/3/26. Urine 1 c.c. Albumen negative ? to nitric acid test. Micro:- nil abnormal.

9 a.m. 3/4 c.c. D.T. subcutaneously (.3 unit).

12/3/26. Urine 3 c.c. nil abnormal chemically or microscopically.

4 p.m. 2 c.c. D.T. intraperitoneally. (.64 unit).

13/3/26. Urine 10 c.c. Albumen, a distinct trace to nitric acid test. Micro:- nil abnormal.

11 a.m. 4 c.c. D.T. intraperitoneally (1.33 units).

15/3/26. Urine (2 days) 16 c.c. nil abnormal chemically or microscopically.

3 p.m. .7 c.c. D.T. intraperitoneally (1 unit).

16/3/26. Urine 2 c.c. nil abnormal chemically.
Micro:- A few epithelial cells, two granular casts.

2 p.m. .7 c.c. D.T. intraperitoneally (1 unit).

19/3/26. Urine (3 days) 8 c.c. nil abnormal chemically.
Micro:- A small number of pear shaped epithelial cells (bladder ?), no casts.

20/3/26. Urine 1 c.c. Albumen, a faint trace to nitric acid test. Micro:- Nil abnormal.

11 a.m. killed.

P.M.

Blood clot in pericardium.

Spleen .32 gram. Congestion.

Right Kidney .70 gram. Left Kidney .60 gram.

$$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{1.30}{90.5} = .014.$$

The kidneys showed a faint mottling on the capsular surface. They were pale yellow in colour and were not congested.

Liver nil abnormal.

Lungs: nodules of yellowish, cheesy material were scattered throughout both lungs.

Microscopic examination:-

Lungs:-
Numerous gram positive diplococci in the caseous areas. Pneumococci on culture.

Liver:-
Congested.

Spleen:-
Congested. Prominence of endothelial cells.

Kidneys:-
There was slight swelling of some endothelial cells of the glomerular tufts with disappearance of some endothelials. The capillaries were not congested. Just a few polymorphs and slight connective tissue increase could be made out between the capillaries, between which there was also a very small amount of hyaline material. There was slight local deficiency of the epithelium covering the tuft here and there, but for much the greater part it was present and not apparently altered. Some convoluted tubules showed slight cloudy swelling with occasional nuclear degeneration and catarrh of a very few cells.

There was just a very small amount of fat in the epithelium of a small number of cells of the convoluted tubules.

There was a very slight round celled infiltration diffusely between tubules of the cortex.

The pneumococcal infection of the lungs has of course to be remembered in assessing results.

Summary.

Very slight changes in both glomeruli and tubules. Little could have been made of this experiment alone, but it fits in with the rabbit experiments, where the later stages tended to show both glomerular and tubular changes, with, as time went on, a tendency to the equalisation of these.

Rat 13.

Healthy white rat. Weight 99.5 grams.
Urine before injections (3 examinations) nil abnormal chemically or microscopically.

10/3/26. 1 p.m. 1/2 c.c. D.T. intraperitoneally (.2 unit).

11/3/26. Urine 3 c.c. trace of albumen to nitric acid test. Micro:- A few leucocytes and R.B.C., one hyaline cast.

9 a.m. 3/4 c.c. D.T. intraperitoneally (.3 unit).

2 p.m. 3/4 c.c. " " (.3 unit).

12/3/26. Urine 2 c.c. Albumen faint trace to nitric acid test. Micro:- One or two epithelial cells, one or two hyaline and granular casts.

4 p.m. 2 c.c. D.T. intraperitoneally (.66 unit)

13/3/26. Urine 10 c.c. Albumen very faint trace to nitric acid test. Micro:- Nil abnormal.

11 a.m. 4 c.c. D.T. intraperitoneally (1.33 units)

15/3/26. Urine (2 days) 7 c.c. nil abnormal chemically or microscopically.

3 p.m. 4 c.c. D.T. intraperitoneally (1 unit).

16/3/26. Urine 1 c.c. Albumen negative ? to nitric acid test. Micro:- No cells, two granular casts,

1 p.m. 2 c.c. D.T. intraperitoneally (1 unit).

19/3/26. Urine (3 days) 6 c.c. Albumen trace ? to nitric acid test. Micro:- Nil abnormal.

20/3/26. Urine 2 c.c. Albumen positive to nitric acid test. Micro:- Two epithelial cells, one granular cast.

11 a.m. killed.

P.M.
Some blood clot in pericardial sac.

Right Kidney .58 grams. Left Kidney .67 gram.

$$\frac{\text{Kidneys}}{\text{Body WT.}} = \frac{1.25}{99.5} = .013.$$

Spleen, .32 gram. Congested.

Liver, nil abnormal.

The Kidneys were pale.

Microscopic Examination:-

Spleen:-
Congestion. Slight prominence of pulp endothelial cells.

Liver:-
Nil abnormal.

Kidneys:-
The glomeruli were congested and their endothelial nuclei unusually large, but darkly staining. The connective tissue between the loops of the tuft was increased. The epithelium covering the tuft showed occasional slight localised loss and a few of the capsular spaces contained small globules of albuminous material. In the interstitial tissue, there were one or two cellular patches, but these were not regarded as due to the injections. The endothelial cells of the capillaries of the intertubular plexus were rather prominent and there was often a little hyaline or fibrillar connective tissue around them.

The tubules showed a moderate degree of catarrh. The epithelial nuclei stained rather poorly, and both they and the cytoplasm were swollen, sometimes greatly swollen.

Casts were noted in a number of the tubules.

No fat was found anywhere.

Summary.

In these rats, there was difficulty in assessing the degree to which alterations present were due to the injections. We are inclined to think that the alterations produced are similar to, though slighter than, those in the rabbits. The slight fibrosis in the glomeruli seems likely to have preceded the injections, the earliest of which was only ten days before death.

The rat is, of course, recognised to be relatively very insusceptible to diphtheria toxin.

Discussion of Changes found with Diphtheria Toxin.

The fundamental nature of the changes is, as expected, identical to the nature of the changes with streptococcal toxin. The same sequence is observable. First there are endoglomerular alterations. These are followed by epiglomerular (the endoglomerular intensifying meantime). Then at a time when albuminous exudate in the capsular space indicates a hyper-permeability of the glomeruli, severer tubular changes set in. The larger number of experiments with repeated doses which we have performed with this toxin served to put this last point on a firmer basis. The more prolonged the experiments, the greater was the tubular damage, especially relatively to the glomerular damage. There is no need to recapitulate the explanation already given of this sequence.

No claim whatsoever is made for an identity in the details of the damage inflicted. Indeed, the minor differences are sufficiently distinctive to allow of an accurate differential diagnosis between the two histological pictures. This is particularly the case in the glomeruli. Both poisons tended to cause congestion there, which was in turn succeeded by necrosis. The streptococcal toxin, however, tended to produce disappearance of the endothelial nuclei by swelling and chromatolysis, whilst the diphtheria toxin caused a remarkable degree of karyorrhexis, and to a less extent pyknosis.

"Blood-cysts" in the glomeruli have been described in the literature in diphtheria toxin nephritis by Lyon, Faber and Leiter. These were

found in two of our diphtheria toxin rabbits, and also in one rabbit (Rabbit T) receiving injections of both diphtheria toxin and streptococcal toxin.

The literature on experimental nephritis, already reviewed, gave similar results to those we have found.

We have thus found that two of the most typical powerful toxins are adapted to produce acute nephritis. The mechanism indicated by the nature of the sequence of changes is such as frees us from the necessity of assuming any special selective quality of the toxins towards the kidneys. At the same time, it apparently broadens the etiological factors in nephritis to include all toxins, a somewhat confusing conclusion in view of the very special role already allotted to the streptococcus.

A little further consideration indicates that this contradiction is not necessarily entailed. Only a certain small group of organisms produce powerful exotoxins. These alone are fitted to produce acute nephritis by the mechanism being considered. Staphylococci, coliform organisms, and many of the ordinary pus-producers do not fulfill the requirements. Such organisms as diphtheria bacilli, streptococci and tetanus bacilli are however suitable. Of these, the diphtheria and tetanus toxins have well known powerfully selective actions on other tissues (heart, nervous tissues, etc.), and it is the less surprising that they should not usually produce nephritis with concentration sufficient to cause death from other causes. No such striking selectivity is evidenced by streptococcal toxin, and this toxin probably owes its special relationship to nephritis, not to the presence of a selective action on the kidney, but to an absence of marked selective action elsewhere.

Moreover, the endotoxic factor, which is probably present also in most cases of acute nephritis, will be absent in diphtheria and tetanus, for it is accepted that these diseases are very rarely septicaemic. Opportunity therefore for the trapping and lysis of organisms in the glomeruli will usually be lacking.

Acute Experiments with Morgan Bacillus No. 1.

This organism was chosen at random from amongst those not supposed to be specially promising for the production of acute nephritis. A preliminary experiment with a filtrate of a 5 day Broth culture failed to produce any significant changes anywhere in the rabbit's kidneys. It did not seem that exotoxin was produced in sufficient quantity to do any damage. Indeed, when the rabbit was killed, it did not seem ill. This was 36 hours after the injection of 8 c.c. of the filtrate.

Two rabbits were then injected with the broth containing the living bacilli (and any exotoxin that might be present). It was to be anticipated on the view we have put forward that these kidneys might show some degree of change, due to the endotoxin produced by the lysis of organisms in the glomeruli.

It was to be anticipated, therefore, that either no significant changes would be found, or that chiefly glomerular alterations would be noted. These, in view of the small amount of endotoxin the organisms probably produce would be comparatively slight unless a suppurative nephritis was set up. Death, if it took place, would be due to general peritonitis from the local multiplication of the injected organisms (intraperitoneal injection).

Rabbit W.

Healthy rabbit. Weight 930 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

6/10/26. 1 p.m. 1 c.c. Morgan b. No. 1 broth intraperit.

7/10/26. Urine 5 c.c. nil abnormal chemically or microscopically.

10 a.m. Died.

P.M.
Commencing peritonitis.

Right Kidney 4 grams. Left Kidney 4 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{8}{930} = .009.$

Spleen .7 gram.

Microscopic Examination:-

Liver;-
Congestion only.

Spleen:-
Congestion only.

Kidneys:-
No organisms were seen anywhere in gram-stained sections.
The glomeruli were very congested. The endothelial nuclei were swollen and appeared here and there to be rather numerous. In some tufts there were considerable numbers of infiltrating small round cells (nearly equal in number to the endothelial cells). There were a few polymorphs in some of the tufts. A few endothelial nuclei were breaking up.
The epithelium covering the tufts was in most cases intact but was often swollen. The capsular space was usually empty but a few spaces showed albuminous material and just these glomeruli showed partial loss of the covering epithelium or great swelling of it. A few of the glomeruli, especially the more extremely cellular ones, showed diminished vascularity.
The epithelium of the parietal aspect of the capsule was sometimes rather prominent.
There was some congestion of the vessels of the cortex.
The convoluted tubules showed slight swelling of the epithelium lining but on the whole were remarkably healthy.

No fat was seen anywhere.

Microphotograph 10.

Summary.

Fairly marked endoglomerular changes, slighter epiglomerular changes. Very little tubular change indeed. Cellular infiltration of glomeruli.

Rabbit Z.

Healthy baby rabbit (5 to 6 weeks old). Weight 390 gms. Urine before injections (4 examinations) nil abnormal chemically or microscopically.

11/10/26. 1 p.m. 2 c.c. Morgan b. No. 1 broth intraperit.

12/10/26. 9 a.m. Died. (No urine obtained since injection).

P.M.

The Kidneys were congested and slightly oedematous.

Right Kidney 1.6 grams. Left Kidney 1.7 grams.

$$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{3.3}{390.} = .009.$$

No naked eye changes in other organs.

Spleen .45 gram.

Microscopic Examination:-

Spleen and Liver, slight congestion.

Kidneys:-

All the vessels, including these of the glomerular tufts, were greatly congested. The tufts showed a moderate degree of round celled infiltration, and great endothelial swelling with disappearance of a few endothelial cells. A few polymorphs were present.

The epithelium covering the tufts was swollen, but there was no exudate or cellular material in the capsular spaces.

There were no interstitial or tubular changes.

No fat was observable anywhere.

Summary.

These two experiments with the Morgan bacilli No. 1 and any toxin it had produced in the broth show two distinct but not unexpected differences from the results with diphtheria or streptococcal toxin. Firstly the endoglomerular alterations, though, as before, the chief ones, are not so marked as with heavy (single fatal) doses of the other substances, and have not (save in a few tufts in Rabbit W) reached the point where there is any appreciable effect on the covering epithelium.

In the second place, amongst such changes as are present within the tufts, cellular infiltration takes a much more prominent part than with the toxins. This infiltration is both round celled and polymorphic, though chiefly the former.

The difference in degree of glomerular damage is in accordance with expectations, and the greater cellular infiltration of the tufts may possibly be related to the actual presence of organisms in the injected material, and therefore in the glomerular tufts.

No organisms were found in the tufts microscopically, but bacterial embolism and lysis seems the only possible explanation of the results.

Chronic Experiments.

The next three experiments were once more attempts to produce chronic changes in the rabbit's kidneys. The two experiments just detailed had shown that the Morgan bacillus was not entirely without action on the kidneys, and this or other organisms were therefore used in an attempt to sustain or augment effects produced by streptococci or diphtheria toxin.

As chronic experiments with streptococci plus toxin had failed already, and as these were the organisms regarded as best adapted for the purpose, we were not very hopeful of success.

We based the effort on the hope that, by varying the type of organism used, it might be more likely that immunisation would be avoided, and that the state of affairs created might therefore in greater degree approach that existing in human beings with chronic septic foci.

Rabbit P.

Healthy rabbit. Weight 930 grams.
Urine before injections (4 examinations) nil abnormal chemically or microscopically.

14/7/26. 10a.m. 1 c.c. Staph. aureus broth intraperit.

15/7/26. Urine 100c.c. Albumen, a faint haze to boiling test, negative to nitric acid test.
Micro:- Nil abnormal.
11 a.m. 1 c.c. Staph. aureus broth intraperit.

16/7/26. Urine 55 c.c. Nil abnormal chemically or microscopically.
4.30 p.m. 2 c.c. Staph. aureus broth intraperit.

17/7/26. Urine 40 c.c. Nil abnormal chemically or microscopically.
9 a.m. 2 c.c. Staph. Aureus broth intraperit.

19/7/26. Urine (2 days) 65 c.c. Nil abnormal chemically or microscopically.
1 p.m. 1/2 c.c. Morgan No. 1 broth intraperit.

20/7/26. Urine 30 c.c. Nil abnormal chemically or microscopically.
10 a.m. 2 c.c. Morgan No. 1 broth intraperit.

21/7/26. Urine 30 c.c. Nil abnormal chemically or microscopically.
10 a.m. 1/2 c.c. Haem. Strep. Culture intraperit.

22/7/26. Urine 55 c.c. Nil abnormal chemically or microscopically.
12.30 p.m. 2 c.c. Haem. Strep. broth intraperit.

23/7/26. Urine 40 c.c. Nil abnormal chemically or microscopically.
12.45 p.m. 6 c.c. Haem. Strep. broth intraperit.

24/7/26. Urine 22 c.c. Nil abnormal chemically or microscopically.
11 a.m. 4 c.c. Staph. aureus broth intraperit.
2 c.c. Strep. Haem. broth intraperit.

26/7/26. Urine (2 days) 60 c.c. Nil abnormal chemically or microscopically.
11.45 a.m. .001 unit D.T. (diluted) intraperit.
12.45 p.m. .002 " " " "
2.30 p.m. .002 " " " "

27/7/26. Urine 105 c.c. Nil abnormal chemically or microscopically.
3 p.m. .002 unit D.T. intraperit. (in 70 c.c. hypertonic saline).

28/7/26. Urine 45 c.c. Nil abnormal chemically or microscopically.
1.15 p.m. .002 unit D.T. Intraperit. (in 60 c.c. hypertonic saline).

29/7/26. Urine 110 c.c. Nil abnormal chemically or microscopically.
3.30 p.m. .002 unit D.T. intraperit. (in 110 c.c. normal saline).

30/7/26. Urine 100 c.c. Nil abnormal chemically or microscopically.
Died this morning.

P.M.

No injected fluid found in peritoneal cavity, but a general peritonitis was present.

Spleen small and pink.

Liver Coccidiosis.

Kidneys- nil abnormal naked eye.

Right Kidney 3.95 grams. Left Kidney 3.5 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{7.45}{930} = .008.$

Microscopic Examination:-

Liver:-
Coccidiosis confirmed.

Spleen:-
No important change.

Kidneys:-
No notable changes, acute or chronic, glomerular, tubular or interstitial were found. Often the glomeruli appeared to contain a little excess of round cells, particularly at the points of entrance of afferent arterioles These arterioles were sometimes a little thickened, with a little round celled infiltration around them, and rather larger branches of the renal arteries were semetimes distinctly thickened. Only occasionally did a glomerular show any deficiency of the epithelium covering it and a trace of albumen in the capsular space.

There was no fibrosis in the tufts or elsewhere.

The endothelium of the capillaries between the tubules showed rather prominent dark staining nuclei. The glomerular endothelium was unaltered.

The tubules seemed unaltered and healthy.

Congestion was only very slight throughout the organs.

No fat was detectable anywhere.

Rabbit 10.

Baby Rabbit (about 6 weeks old). Weight 420 grams. Urine Before injections (4 examinations) nil abnormal chemically or microscopically.

12/10/26. 4 c.c. Scarl. Strep. Broth A intraperit.

13/10/26. Urine:- nil abnormal chemically or micro.

15/10/26. Urine (2 days) nil abnormal chemically or micro.
6 c.c. Scarl. Strep. Broth A intraperit.

16/10/26. Urine, nil abnormal chemically or micro.
6 c.c. Scarl. Strep. Broth A intraperit.

20/10/26. Urine (4 days) nil abnormal chemically or microscopically.
8 c.c. Scarl. Strep. Broth A intraperit.

21/10/26. Urine, nil abnormal chemically.
Micro:- One or two hyaline casts.
1 c.c. Morgan B. No. 1 Broth intraperit.

23/10/26. Urine (2 days):Albumen, trace to nitric acid and boiling tests.
Micro:- A few cells, one or two granular casts.
1 c.c. Morgan B. No. 1 Broth intraperit.

27/10/26. Urine (4 days), nil abnormal chemically.
Micro:- A few epithelial cells.
10 c.c. Scarl. Strep. Broth B. intraperit.

30/10/26. Urine (3 days), nil abnormal chemically or micro.
20 c.c. Scarl. Strep. Broth B. intraperit.

2/11/26. Urine (3 days) Albumen, trace to boiling; negative to nitric acid test.
Micro:- Crystals, no cells, no casts.
2 c.c. Morgan B. Broth intraperit.

3/11/26. Urine:- Albumen, trace to nitric acid and boiling tests.
Micro:- One epithelial cell, a doubtful granular cast.

8/11/26. 25 c.c. Scarl. Strep. Broth A intraperit.

9/11/26. Dead this morning.

P.M.

Kidneys, Spleen and Liver congested. Spleen rather large.
Slight localised peritonitis.

Right Kidney 2.5 grams. Left Kidney 2.5 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{5}{420} = .012.$

Microscopic Examination:-

Spleen and Liver - nothing to note.

Kidneys:-

The vessels throughout the organ were exceedingly congested. The glomeruli especially were very congested, all the capillaries being distended with blood. There was no thickening of the capillary walls, but there was some round cells, and to a lesser extent some polymorpho-nuclear, infiltration of a number of the tufts. The endothelial nuclei were rather swollen. The tuft epithelium had in some cases disappeared, in most it was present but swollen. A few of the more affected glomeruli showed a little albumen in the capsular spaces.

The convoluted tubules and broad part of the ascending limb of the loop of Henle, showed moderate but widespread degeneration of their lining epithelium. This took the form of a foamy transformation of the cell cytoplasm, little more being evident often than the nucleus and the cell membrane. The nuclei were normally shaped and stained just a shade faintly in most cases, but every here and there a few nuclei had disappeared. Occasionally, there was a little catarrh.

There were only a very few healthy tubules, and those with their darker eosin staining, showed in sharp contrast to the affected ones. These unaffected tubules were early first convoluted tubules.

There was a very little fat in one or two isolated convoluted tubules, and a little in one or two of the larger collecting tubules.

Summary.

This experiment can be explained as again showing chiefly acute glomerular changes, with abnormal glomerular permeability and later tubular changes. For all these, the streptococcal broth was probably mainly responsible.

There is no hint of commencing production of chronic changes (28 days duration of experiment).

Rabbit U.

Healthy rabbit. Weight 1400 grams.
Urine before injections (4 examinations), nil abnormal chemically or microscopically.

6/8/26. 10 a.m. 1/2 c.c. No. 3 Strep. Toxin intraperit.

7/8/26. Urine 20 c.c. Nil abnormal chemically or micro.
10 a.m. 1 c.c. No. 3 Strep. Toxin intraperit.

8/8/26. Urine 25 c.c. Nil abnormal chemically or micro.

9/8/26. Urine 30 c.c. Nil abnormal chemically or micro.
10 a.m. 1 c.c. No. 3 Strep. Toxin intraperit.

10/8/26. Urine 31 c.c. Nil abnormal chemically.
Micro:- A few epithelial cells, and granular casts.
10 a.m. 1 c.c. No. 3 Strep. Toxin intraperit.

11/8/26. Urine 28 c.c. Albumen, trace to nitric acid and boiling tests. Micro:- A few epithelial cells, a granular cast.
10 a.m. 1 c.c. No. 3 and 1 c.c. No. 2 Strep. Toxin intraperit.

12/8/26. Urine 20 c.c. Albumen positive to nitric acid and boiling tests.
Micro:- Some epithelial cells and granular cast.
10 a.m. 1 c.c. No. 2 Strep. Toxin intraperit.

13/8/26. Urine 27 c.c. Albumen positive to nitric acid test, doubtful to boiling test..
Micro:- A few epithelial and granular casts.
10 a.m. Suspension in saline of one agar slope of staphylococcus aureus (from healthy mouth) intraperitoneally).

14/8/26. Urine 35 c.c. Albumen trace to nitric acid and boiling tests. Micro:- 1 epithelial cell, a few hyaline and granular casts.
10 a.m. 1 c.c. No. 2 Strep. Toxin intraperit.

16/8/26. Urine (2 days) 40 c.c. Albumen trace to boiling test, negative to nitric acid test.
Micro:- No cells, one or two granular casts.
10 a.m. 1 c.c. No. 2 Strep. Toxin and 8 c.c. Morgan B. Broth intraperit.

17/8/26. Urine 37 c.c. Albumen positive to nitric acid and boiling tests. Micro:- A few epithelial cells and a moderate number of hyaline and granular casts.
10 a.m. 20 c.c. Morgan b. Broth intraperit.

18/8/26. Urine 32 c.c. Albumen positive to nitric acid and boiling tests. Micro:- A few epithelial cells and granular casts.
10 a.m. 1/8 agar slope of Strep. Haem. (from sore throat case) intraperit.

19/8/26. Urine 20 c.c. Albumen trace to nitric acid and boiling tests. Micro:- A few epithelial cells, no casts.
9 a.m. 30 c.c. Morgan Broth intraperit.

20/8/26. Urine 30 c.c. Albumen negative to nitric acid test, trace to boiling tests.
Micro:- An epithelial cell, no casts.
10 a.m. 1/2 agar slope of Strep. Haem. (from sore throat case) intraperit.

23/8/26. Urine (2 days), 25 c.c. Albumen trace to boiling and nitric acid tests.
Micro:- Nil abnormal.
10 a.m. 3 c.c. Scarl. Strep. Broth A intraperit.

24/8/26. Urine 28 c.c. Albumen trace to boiling and nitric acid tests. Micro:- A few epithelial cells and granular casts.
10 a.m. 5 c.c. Scarl. Strep. Broth A intraperit.

25/8/26. Urine 10 c.c. Albumen trace to boiling and nitric acid tests. Micro:- No cells, a few granular casts.
10 a.m. 9 c.c. Scarl. Strep. Broth A intraperit.

26/8/26. Urine 15 c.c. Albumen positive to boiling and nitric acid tests. Micro:- A few epithelial cells and granular casts.
1 p.m. 30 c.c. Scarl. Strep. Broth A intraperit.

27/8/26. 10 a.m. Died.

P.M.

General peritonitis present.
Spleen and Liver congested.

Kidneys show fine but distinct pitting of surface. Cut surface of the medulla is oedematous.
The kidneys are not reduced in size.

Right Kidney 6.8 grams. Left Kidney 7 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{13.8}{1400} =$ .010.

Microscopic Examination:-

Kidneys:-

These showed a more marked degree of chronic change than any other yet found in the series. Nevertheless, the description will be immediately followed by a description of similar appearances in a rabbit whose first injection was so recent (under 4 days before) that one is bound to put down the type of change found as spontaneous.

The glomeruli were almost all slightly over-cellular. The endothelial cells were small and pyknotic and there was a varying number of infiltrating small round cells. A few fibroblasts were also present in some tufts. There was sometimes a very slight inter-capillary increase of fibrous tissue, and often there was some shrinkage of the tufts. The glomerular capillaries were, in a good many cases, narrowed. There was some lobulation of some tufts. The epithelium covering the tufts was atrophic, but was in most cases complete. The epithelium covering the parietal aspect of the capsule was also very flat, and one found a little laminated fibrous tissue around some of the tufts. The basement membrane of the capsule was often thickened. A few capsular spaces showed a little albuminous material or a few epithelial cells. In one case, epithelial cells on the outer aspect of the capsule formed a sort of commencing crescent. The degree to which the glomerular tufts were affected varied considerably, but the chronic change was always slight. In some a portion of the tuft showed merely swelling of the endothelial cells, whilst another part showed more marked cellular infiltration.

The walls of all arterioles in the cortex were slightly but distinctly thickened, the thickening being chiefly in the media and adventitia. There was a zone of young and very cellular connective tissue (round celled) around the larger vessels. The afferent arterioles of the glomeruli showed slight thickening and a little round celled infiltration around them. There was even sometimes a very slight round celled infiltration between the tubules in relation to the intertubular plexus of the cortex.

There was thus a cellular infiltration of the interstitial tissues, slight, and related thiefly to bloodvessels, especially, perhaps, to afferent arterioles. The walls of the bloodvessels were also slightly thickened.

Here and there in the sections, however, were areas in which there was a greatly increased and definitely focal cellular infiltration of the interstitial tissue with some fibrosis. It is such areas, wedge-shaped and underlying the capsule, that cause the naked eye depressions of the cortical surface. Similar areas, however, appeared in the substance of the cortex and in the boundary zone. These deeper patches appeared from their shape to be obliquely cut portions of wedges which also really reached the capsular surface.

Sometimes these areas were obviously related to a thickened vessel with perivascular infiltration, and usually to a vessel of such size and situation that it was likely that its area of distribution corresponded more or less to the area of focal inflammation.

The infiltrating cells were almost all small round cells and they separated the tubules widely. Their arrangment was to a certain degree concentric around the tubules. The tubulus in such cases were never normal, and showed one of two varieties of atrophic appearance. Some were small and lined by healthy cells, which were, however, of low cubical type. Such shrunken tubules had no lumen. These tubules were sometimes differentiated with difficulty from the surmounting round cells. Other tubules were greatly dilated and their lining epithelium was even more flattened, being endothelial-like in appearance. Frequently their lumens contained casts.

The capillary vessels and arterioles within the area were much thickened, with hyaline walls, and very narrow lumen.

The glomeruli within the scar were sometimes not more distinctly affected than the worst of those in the kidney elsewhere. At other times they were smaller and more atrophic, with increased cellularity. Only a small amount of hyaline alteration was observable in these tufts.

The tubular changes outside the focal scars were relatively slight. Many tubules showed only a minor degree of cloudy swelling. Some had a little granular debris in the lumen. A few, especially the early parts of some first convoluted tubules, showed marked catarrh and striking nuclear pyknosis.

Sometimes practically the whole pyknotic epithelium of such a tubule was lying scattered in the lumen.

No fat was found in any part of the organ.

SUMMARY.

Wedge shaped focal areas of round celled infiltration and cellular fibrosis, the glomeruli in these areas being relatively normal, the tubules atrophic or degenerating. The vessels throughout the organ, but more especially within these foci, sclerosed.

Slight tubular and glomerular changes outside the foci described.

Discussion:-

This experiment was designed for the purpose of producing chronic changes. This was the purpose of both the variation and the prolongation of the injections. When we remember that chronic changes similiar to those found here were not got in acuter experiments, and were not obtained in controls, we are greatly tempted to accept the changes as a genuine result of the injections. Such an attitude has been frequently noted in the literature.

A detailed examination, however, of the nature of the changes, shows that they are distinctly more like those of spontaneous nephritis. The changes have a more sharply focal distribution that those in chronic nephritis in man. In the human condition, the lesions are certainly not diffusely uniform, but there is less sharp demarcation into severely affected and almost healthy tissue. Rather there is a tendency for all degrees of change to be represented in different parts of the organ.

The other difference from human nephritis lies in the relatively slight affection of the glomeruli even in the midst of the focal lesions

Roughly, the usual chronic nephritis of man is a chronic and fairly diffuse glomerulo-nephritis. This rabbit's kidneys do not show either a glomerulo-nephritis nor a diffuse nephritis.

It must be admitted, however, that were we to make the comparison with some descriptions of "arterio-sclerotic" kidney in man, very little difference might be distinguishable. This is probably because spontaneous nephritis is largely "arterio-sclerotic".

Our decision that this rabbit showed an example of spontaneous nephritis was eventually determined by the examination of the kidneys of another rabbit. This rabbit had been first injected only between 3 and 4 days before death, and yet its kidneys showed changes identical with those we have been describing. (Compare Microphotographs // 9/2.) It is scarcely conceivable that changes of such an evident chronicity could have been produced in such a short period as elapsed after the first injection.

At the same time, the initial impressiveness of discovering, for the first time, chronic changes, in an experiment designed to produce chronic changes, strengthened our impression that the literature contains many examples of erroneous observations based on a similar source of fallacy.

For the sake of comparison we will record next, the protocol of the other rabbit (Rabbit Y) in which spontaneous changes were found.

RABBIT Y.

Healthy Rabbit. (5 weeks old). Weight 420 grams.
Urine before injections (4 examinations):- Albumen negative to HNO_3 and boiling tests. Micro:- Nil abmormal.

7/10/26.	3.30 p.m. 2 c.c. Scarl. Strep. Broth B. intraper.
8/10/26.	Urine 35 c.c. Alb. neg. to boiling and nitric acid tests. Micro:- Nil abnormal.
	12 a.m. 6 c.c. do. intraper.
9/10/26.	Urine 10 c.c. Alb. neg. to boiling and nitric acid tests. Micro Nil abnormal
	10 a.m. 7 c.c. Morgan No. 1 Broth Intraper.
11/10/26.	Urine (2 days) 8 c.c. Alb. distinct trace to nitric acid and boiling tests. Micro:- Many bacilli: a few epithelial cells; no casts.
	Dead this morning.

POST-MORTEM.

Nil gross in any organ save kidneys, which showed oedema of the medulla and congestion of the cortex, and liver and spleen which were rather congested.

Right Kidney 2·6 grams. Left Kidney 2·4 grams.
Spleen ·5 grams.

$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{5}{420} = .012$

MICROSCOPIC EXAMINATION.

Kidneys.

Two sets of appearances may be separated out - a diffuse recent change, and a focal change of apparently older origin and not related to the injections, the first of which, it may be noted, was given only 3 - 4 days before death.

Diffuse Recent Changes.

The glomeruli were all greatly congested and almost filled the capsular space. The endothelials were often swollen, a few showed karyorrhexis and the number of visible nuclei was often decreased. The tuft epithelium was greatly swollen throughout but was apparently intact. A few spaces contained one or two R.B.C's. There were no interstitial changes.

The convoluted tubules were not markedly affected but a number showed swollen nuclei, a few pyknotic nuclei and some were catarrhal. The tips of the epithilial cells were sometimes broken down into the lumen.

The whole organ was greatly congested. There was no detectable fat.

Chronic Changes.

In at least one localised but fairly large patch of cortex the picture was different.

The glomeruli were shrunken and apparently overcellular, but the cells were mainly shrunken endothelials approximated by the glomerular shrinkage. The capillaries were still premeable but not dilated and there was usually no intercapillary increase of fibrous tissue. The epithelium covering the tuft

was flattened and atrophic. In some cases the tuft had shrunk so as to leave a wide capsular space. The outer aspect of the capsule showed definite fibrous tissue increase with a tendency to a concentric arrangement. In other glomeruli the capsular space was obliterated and the tuft was made out in the midst of cellular connective tissue from which it was demarcated by the persistence in its greater part of the "parietal" epithelium of the capsule. In these adherent tufts alone there was intercapillary increase of fibrous tissue.

The matrix in which these glomeruli were imbedded was a cellular connective tissue in which the tubules also were embedded and fairly widely separated from one another by the connective tissue. The tubules were small with atrophic (cubical) epithelium, and little or no lumen. The epithelial cells showed, however, little signs of degeneration apart from their size. Some others tubules, also small, were lined by an epithelium so flat that they were with difficult-y distinguished from capillary vessels, especially as they contained in some cases R.B.C. It was possible, however, to note all transitions to the more obvious cubical cells, where the lumen also sometimes contained !R.B.C.

No fat was dectectable in these areas.

Microphotographs. /2.

Discussion.

The focal areas show the same changes as Rabbit U and, occurring within 4 days after the first injection, can scarcely be regarded as due to that injection. It would seem certain, therefore, that the lesions here, in Rabbit U, and many similar lesions described in the literature, are not necessarily the direct result of the injections.

Spontaneous nehpritis must be very difficult in-deed to exclude if we take this as an example, for it can evidently be found even in a 5 weeks old rabbit, and even when nothing abnormal is found in the urine before injection.

The acute changes seen elsewhere in this rabbit's kidneys are chiefly glomerular, are due to the injections, and show no unexpected features.

We shall conclude the record of our own experiments with the protocol of the only animal in which an attempt was made to produce changes by feeding.

RABBIT S.

Urine before experiment commenced (4 examinations) Nil abnormal chemically or microscopically.

For 3 months this rabbit was fed with Staphylococcus Pyogones Aureus. One heavy growth from an agar slope was mixed with a small portion of oats and fed to the animal before it received any further food. This was done daily.

At no time was anything abnormal found in the urine chemically or microscopically. (Organisms were not found in the urine).

At the end of this period the rabbit was killed.

P.M.

Nil abnormal in any organ naked eye.

Rigt Kidney 3·6 grams. Left Kidney 3·4 grams.

$$\frac{\text{Kidneys}}{\text{Body Wt.}} = \frac{7}{850} = \cdot 008.$$

MICROSCOPIC EXAMINATION.

Kidneys.

There was some congestion of the inter-tubular plexus and of the veins. There was some round celled infiltration of the tufts, and a few polymorphs were also present.

The capsular spaces were normal, and the eptihelium "parietal" and "visceral" was unaltered.

No changes were noted in the tubules or interstitium. No fat was found anywhere.

Conclusion. The results were thus completely negative.

Summary of general Conclusions as to the Etiology and Course of Nephritis.

The separate recording of details, and grouping of these under different headings, rendered obligatory by our method of discussing the subject in its various aspects, have of necessity widely separated many of the conclusions arrived at. Most of these conclusions have already been set down after consideration of the relevant evidence, and we now propose to gather together the chief points, and to recapitulate in a condensed form our main conclusions as to the etiology and course of the disease. For details the reader will on occasion be referred to the particular part where these are set down.

In section 1, we have argued that there is every reason to regard as correct the usual hypothesis of a bacterial or bacterio-toxic origin for practically all non-suppurative nephritis. Further, it is possible that at least most cases are due to the combined action of the bacteria concerned and of the toxins they produce.

The high percentage of cases in which careful investigation may reveal a bacteriuria in both acute and chronic nephritis suggests that toxins are concerned alone only in a small percentage of cases.

Even on theoretical grounds, it is unlikely that the action of the bacteria is secured by anything in the nature of focal multiplication in the kidneys. Such a process would tend to produce a suppurative condition. The acute nephritis we are considering is anything but suppurative. Indeed, the remarkable feature which sets its acute form apart from the other acute inflammations is the absence, or at least the insignificance, of polymorphonuclear infiltration.

On other grounds also it is not likely that the difficulties which undoubtedly exist in solving the etiological problem would be nearly so formidable as they are, if such multiplication took place. Bacteria would be observed in the urine and in post-mortem kidneys in great numbers, and with a constancy and ease which would not require special methods for their demonstration. Besides, a condition has been described in which such multiplication in the kidneys does take place, and it is not the acute non-suppurative nephritis we are dealing with (Campbell and Rhea. See p. 63.)

Pursuing this point further, we can imagine only one other way in which bacteria may be directly implicated, namely by bacterial embolism with lysis in the kidneys. The usual trap for the organisms

must for anatomical reasons be the glomeruli. Experiments with bacteria have shown that where results were obtained with these without toxins, the kidneys showed a preponderatingly glomerular incidence(p. 253.)

We shall for a little confine our attention to acute nephritis. It is obvious that if the causal factors are bacterial embolism with glomerular lysis plus the action of the exotoxin, the suitability of various bacteria for producing acute nephritis must vary enormously. Different bacteria differ strikingly in the potency both of their endotoxin and of their exotoxin. Moreover, the endotoxic factor can only rarely operate in diseases which, however severe, are but rarely septicaemic (e.g. diphtheria). Comparatively few organisms produce powerful exotoxin. Of these, the majority usually produce pure toxaemias (such as diphtheria and tetanus), and are not so suitable, on our theory, for producing nephritis, for the endotoxic factor, resulting from bacterial embolism, drops out. Moreover, in most of them, again including diphtheria and tetanus, the toxin has a well known special action on other important tissues which will tend to cause death before unselective or less selective renal complications can develop.(p. 249 .) One powerful exotoxin, however, is without such marked selective action elsewhere and that is the toxin produced by certain varieties of streptococcus(e.g. streptococcus of scarlet fever.) Moreover, this organism is one

which is frequently septicaemic, so that here the endotoxic factor need not be lacking. It is true that the ordinary case of scarlet fever is regarded as analogous to one of diphtheria, and therefore a toxaemia rather than a septicaemia, but the numerous streptococcal "complications" of scarlet fever demonstrate that even here septicaemia cannot be infrequent.

Other organisms - coliform, staphylococci, etc. which abundantly fill the role as regards the frequently septicaemic nature of infection by them, do not produce as powerful exotoxin; nor, probably is their endotoxin so very potent. At least it is striking how infrequently severe acute illness is caused by many of them in cases where they do not settle down and multiply in the viscera, producing either ordinary pyaemia, or, in cases like typhoid, special pictures by attacking selectively certain sites.

These considerations narrow down the theoretical "optimal" method of producing acute nephritis considerably. They suggest, in effect, that by far the most suitable method for its production is by the combined action of a streptococcus and its toxin. On the other hand, they suggest that the renal action of other toxins will be milder either because death is liable to occur from selective changes elsewhere (diphtheria etc.)

or because the organisms are not in the bloodstream (diphtheria etc.)

Other bacteria will fail for different reasons. They may be deficient both in endotoxin and exotoxin, although they are causing a septicaemia (e.g. b. coli). The changes such organisms produce in the kidneys may be of the same nature as acute non-suppurative nephritis, but will, in severity, fall short of it. Undoubtedly, such organisms can and do attain a very high virulence, but in them this is known to be associated, not always so much with a raised toxic titre as with the acquisition of the power of metastatic multiplication. Mild, or even fairly severe, infections with these will thus fail to produce fully developed non-suppurative nephritis. Severer infections may produce a suppurative nephritis from metastatic multiplication in the kidneys.

This theoretical reasoning is borne out by the results of bacteriological investigations in human cases, as may be seen in Section 1 (see Summary Section 1 p.67 etc.). Clinical and post-mortem evidence both point to the streptococcus as the commonest of the causes of acute nephritis. Other organisms may cause it but only in overwhelming dosage, and in that dosage they at least as often produce suppurative nephritis instead. (Section 1 P.M. evidence p.28 etc.).

Section 2 further confirms the hypothesis, because streptococcal toxin was found to produce the experimental picture which most nearly resembles acute nephritis in man. Diphtheria toxin was almost as efficient, however, but its selective effects in other organs (heart, nervous system) together with the more constant absence of bacteriaemia, explain its inefficiency as a cause of human cases.

So far, it will be noted, the trend of these observations has been to inculpate the streptococcus, without necessarily falling back on a special selectivity for the kidneys on the part of that organism. It will be necessary to show next that, granting such a bacteriaemia and toxaemia as the streptococcus produces, there are reasons why special lesions may be expected in the kidneys.

Supposing for a moment that we assume that we are correct so far, and that streptococci and their toxins are the usual causes of acute nephritis, what incidence and sequence of the renal changes may be expected?

Both of our alleged factors have to be considered in relation to the structure and function of the kidney. Bacterial emboli will naturally be trapped for the most part in the glomeruli. These will therefore be the site of lysis, of endotoxin production, and therefore of maximum damage. Injury to the tubules by organisms which are trapped later in

the circulation (in the intertubular plexus) cannot be excluded, nor can some injury due to organisms which have escaped glomerular lysis and have passed into the tubules with the filtrate. Both of these are, however, probably minor factors.

The Morgan bacillus experiments on pp.250-254 show mainly glomerular lesions and so confirm this supposition as to the site of action of bacterial emboli in the kidneys. Similarly, the literature on the subject, in which experiments with a great variety of organisms are recorded, points to a mainly glomerular lesion (pp. 160-168 summarised p. 167-8).

Turning to the toxins, we expect a similar initial localisation of the severer lesions. Toxins probably belong to a class of substances (colloids) which do not pass the normal glomerular filter. They should therefore in behaviour and in incidence of damage be in striking contrast to simple chemical poisons (crystalloids) to which the normal glomerular filter is permeable (pp. 82-85. pp. 202-205). The transference of an enormous bulk of diluent from the blood circulating through the tufts to the filtrate in the tubules should greatly concentrate toxins in the glomeruli. Such toxins are not filterable so long as the tufts remain normal. When the blood containing the concentrated toxins passes on to the intertubular plexus, fluid reabsorbed from the tubules should again dilute

this toxin almost to its previous concentration, so that the glomeruli alone, of all sites in the body, are from their very function exposed to a greatly heightened concentration of the toxin. The rise in the concentration is such as to be likely to overshadow any greater sensitiveness to the toxin of the highly specialised epithelial cells of t-he tubules . This variation in the concentration of toxins would therefore lead us to expect initial endo-glomerular lesions. We should expect further, to find these affecting in a short time the epithelium covering the tuft. When this damage to the covering epithelium has progressed to a sufficient degree, we should expect the damaged glomerular filter, consisting of the endothelium and epithelium with supporting basement layer in the capillary wall, to behave less selectively, and to allow colloids, such as albumen and toxins to pass through. The histological picture - albumen in the capsular space, and in the urine - abundantly proves permeability to albumen at least and it is a fair inference that some, at any rate, of the toxin accompanies it. Such toxin as passes will be concentrated in the tubules by reabsorption from the filtrate,thus exposing the tubules to the action of this concentrated toxin. The tubules, therefore, will, at this later stage, begin to show a special and notable degree of

damage. Meanwhile, the glomerular changes need not continue to intensify, for the same process of permeability to toxin which exposes the tubules to increased damage decreases the capacity of the glomeruli for concentrating toxin. If complete permeability of the glomeruli to the toxin were once established, this capacity would be wholly lost. This detail is of some importance. The view we are putting forward professes to be based on a broad general principle. It claims therefore to represent a probable sequence in all cases of acute non-suppurative nephritis: or, at least, if there are exceptions, reasons must be given for excluding them from the mechanism. For example, if the theory necessarily involved the prescence of predominant glomerular changes in all cases post-mortem, it would be falsified immediately by the actual facts observed. It does not involve this, however; for as we have just shown, it leads us to expect that in later stages tubular changes may predominate.

A further reason why the initial glomerular lesions may diminish in intensity may be an early dropping out of the septicaemic and embolic factors, leaving only the toxaemia.

When we seek post-mortem confirmation of this theory, we find that the most fulminant cases of acute nephritis doe generally show predominant, or even almost pure, glomerular changes. (p. 77). However, it is equally obvious that acute nephritis kidneys observed post-mortem do not invariably show a predominantly glomerular change. They show all degrees of combination of glomerular, tubular and interstitial damage. It is possible, indeed, to classify them into 3 types, according to which lesion is predominant post-mortem; but it is universally admitted that this is a classification of convenience, indicating, as said, simply a predominance and not three sharply defined classes. It is usual to seek for a difference in cause to explain these different types. In view of the gradual merging of the classes into one another, is it not equally logical to seek to explain many as being different stages?

Of the three groups, the smallest, the interstitial, is the best defined, and the nearest to an entity. It accordingly is the one where some difference in the actual causal mechanism should most naturally be suspected. The glomerular and the tubular shade so gradually into one another that the explanation of difference in phase is the more plausible one.

As it is difficult to find any sure method of tracing the sequence of changes in any particular post mortem kidney, we have to turn to experimental nephritis for an opportunity to examine cases of identical origin at successive stages.

All our early diphtheria toxin cases (p.248) and all our early streptococcal toxin cases (p.202) showed glomerular changes predominant or even alone, and the endoglomerular appeared slightly before the epiglomerular.

Later stages showed a gradual decrease of this predominance, and an increase of the tubular change,- but never before there was some indication that the glomeruli had become abnormally permeable, at least to albumen.

The literature on snake venom (p.153) and on diphtheria toxin (p.155), the most commonly used toxins shows a similar predominance of glomerular changes in the earlier stages; some writers referred to have even noted increased prominence of the tubular lesions in later stages (p.154).

Thus post-mortem evidence, as far as regards the glomerular and tubular types, is not in conflict with our view as to the sequence, and experimental evidence gives it very strong support. We will deal with the special position of acute interstitial nephritis shortly.

An indirect method of testing the theoretical basis of our view is furnished by experimental chemical nephritis and occasionally by chemical cases of nephritis occurring in man. In such cases our theory would lead us to expect that for the production of glomerular lesions a dosage higher than that required to produce tubular lesions would be required. Simple crystalloid chemicals will filter through the tufts and will not be concentrated there, but will be greatly concentrated in the tubules. Tubular lesions should therefore predominate from the outset. This should be a uniform effect of all simple crystalloid chemicals, because the degree of the tubular concentration is so high that it is not likely to be balanced by any possible selectivity for the glomerular endothelium (pp. 89-91). The fact that some chemical poisons (e.g. cantharidin) have been usually regarded as predominantly glomerular was a strong point therefore against our assumption. Careful and critical examination, however, of the literature dealing with 13 of the more commonly used chemical poisons showed that in all cases most observers report a predominant tubular incidence. (pp. 91-111 and summary and discussion pp. 146-9).

The 13 poisons included cantharidin and some other chemicals supposed to have a similar action on the glomeruli. Our own experiments with three chemical substances (salts of chromium, lead and iron) showed that the earliest and principal lesions were tubular

in all cases. The results are thus in striking contrast to equally consistent opposing results with toxins, and so confirm in that way the assumptions on which our theory was based.

There is one form of acute non-suppurative nephritis which cannot be explained as representing any phase of the sequence we have just described. A sequence of glomerular, glomerulo-tubular, and then chiefly tubular, nephritis, explains the post-mortem appearances where these are either chiefly glomerular or chiefly tubular, or a fairly balanced mixture of both. It does not, however, explain the rather unusual acute interstitial nephritis. Now, this form shades less into the other two than they do into one another. It has been described as occurring specially in septic cases (p.207). It approaches more nearly than the others to the "acute infectious" nephritis described by Campbell and Rhea (p.63), and to ordinary (pyaemic) suppurative nephritis. We are therefore disposed to regard it as occurring where there is actual multiplication of organisms within the kidneys and as thus representing a link between acute non-suppurative glomerulo-nephritis and acute suppurative nephritis. It represents a condition due less to endotoxic and exotoxic action and more to local bacterial multiplication than do the other forms of acute non-suppurative nephritis. At the same time there is still probably a strong toxic element, and the local multiplication is not equivalent in degree to that in acute suppurative nephritis.

Moreover, the histological picture often suggests a nearer approach to a suppurative process than is found in other forms of acute non-suppurative nephritis. A view similar to ours is held by Parsons (125) who regards interstitial nephritis as "not far removed from pyaemic abscesses".

Another group of acute renal changes requires some special consideration. These are the "toxic" changes seen in cases of sepsis where there is no actual nephritis. These are frequently mainly tubular (p. 82). We would regard these as indicative of an amount of toxin insufficient, even when concentrated in the glomeruli, to produce acute nephritis. The continued action of this dilute toxin is, however, sufficient in many cases of sepsis to cause cloudy or fatty changes in the highly specialised cell of the renal tubules. This is not necessarily a selective change, for a similar type and even degree of change may in the same cases be found in the highly specialised cells of other organs (e.g. liver).

A. Summary of Sequences in Acute Non-suppurative Nephritis (due to Streptococci).

ENDOGLOMERULAR NEPHRITIS. — Bacterial embolism in glomeruli, lysis; production of endotoxin. Toxaemia - concentration of exotoxin by withdrawal of fluid in the glomerular filtrate.

ENDOGLOMERULAR AND EPIGLOMERULAR NEPHRITIS.

(Septicaemic factor drops out.)

Albuminuria (tufts now toxin-permeable).

Some toxin gets to filtrate and is concentrated in the tubules.

Tubular lesions become prominent and intensify.

GLOMERULO-TUBULAR NEPHRITIS.

Glomerular lesions may actually retrogress, if toxin is passing quite freely through very permeable glomerular membranes and so no glomerular concentration is occurring.

TUBULAR NEPHRITIS.

B. Summary of Sequences in Acute Suppurative Nephritis (non-streptococcal.)

1. Tubular degenerative changes, along with degenerative changes of similar degree and type in highly specialised cells elsewhere (e.g. polygonal cells of liver) - due to toxaemia of too low virulence to cause severe damage in glomeruli even on concentration. (Coexisting bacteriaemia is resulting in bacterial lysis in the glomerular tufts but the released toxins are not sufficiently powerful to cause significant glomerular damage.)

2. Suppurative nephritis. Increased virulence of the organisms leads to their focal multiplication in the glomeruli and interstitium, etc.

Turning to chronic nephritis, many of the factors considered in relation to acute nephritis must have equal importance here. Others have not. Probably the action of toxin is of lesser importance here, but it is not excluded. The bacterial embolism and lysis factor is probably more important.

Whilst the predominantly glomerular action of a toxin may diminish in later stages, the site of action of an embolic factor, regarded here as more important, will remain glomerular throughout. This would suggest that the key to progressive renal changes lies mainly in the glomeruli. Pathological evidence shows that where kidneys show only slight evidence of commencing progressive changes (e.g. after influenza etc.) these are mainly localised to the glomeruli. As regards further evidence on this point, we are greatly handicapped by the dearth of assistance from the experimental side. Our review of the literature has convinced us that there is no good evidence that anyone has ever obtained marked progressive changes in animal kidneys by experimental procedures of any kind whatsoever. No one has succeeded in producing genuine contracted kidneys. Numerous observers have claimed to have done so, but the description of the changes produced corresponds in all cases with those of spontaneous nephritis. It is possible that the appearances they found were aggravated or that the localisation in the kidneys was determined by the poison

introduced, but they are not direct sequelae of the earlier alterations produced by the poisons employed (p. 56).

We ourselves have failed to produce chronic changes even when the method of injections was varied from the usual in various ways in order to secure more uniform and continuous absorption (p. 152) or in order to prevent immunisation (p. 255).

There are two possible reasons for this failure. The first is the type of animal used. There is strong evidence that in the majority at least of lower animals, true spontaneous glomerular nephritis is rare (p. 89). It would be interesting to investigate its incidence in monkeys. If it occurs naturally in them, they might prove more suitable for the experimental elucidation of the problem. It is confusing enough to have to investigate the experimental production of a disease in an animal which naturally suffers from the disease in question, but it is not so disheartening as persistent attempts to produce a disease in animals in which numerous failures render it doubtful if it be possible to produce it.

The other possibility is that our views as to a difference in the method and continuity of infection or toxic action in man and in the experiments tried, are correct. We have not successfully countered this difficulty by the methods we have employed, but it is possible that in the future a successful method may be

devised. We believe that the most hopeful method would be one by which in a suitable animal a chronic (preferably streptococcal) septic focus could be produced and maintained.

The man or animal with such a focus is in an entirely different position from the experimental animal into which similar organisms or organisms and toxins are being introduced from the outside, however continuously, because the persistence of the septic focus is in itself an indication of absence of immunisation sufficient to eradicate it.

In minor ways, however, experimental evidence may be of some assistance. It suggests, for example, that lesions in the smaller arterioles may play an important part (literature p. 158 personal experiments p. 215). At least, infiltrations in relation to these arterioles and thickenings of them are often quite distinct even in late stages of acute experiments. Although they cannot apparently be increased in prolonged experiments to cause severe chronic changes, they seem, as far as they go, to be permanent. They are usually accompanied by a slight increase in the cellularity of the glomerular tufts, which also apparently cannot be rendered much more marked by considerable prolongation of the experiments. Nevertheless, these two slight changes taken together may be of some importance in so far as they are the only producable (non-spontaneous) chronic changes in

the kidneys of animals.

(Our own experiments were, it is admitted, in no case sufficiently long to give us the right to regard chronic lesions as non-producable, but we have already seen that even the most prolonged experiments in the literature have given only the most dubious of results).

Moreover, indirectly, the experimental evidence encourages us to negative at least one possible origin of the interstitial changes in chronic nephritis. It is very easy with chemical poisons to produce and sustain severe tubular lesions, and many prolonged experiments of this nature are on record; yet there is no evidence which, when considered critically, shows that even the most marked and prolonged tubular lesions can lead to interstitial overgrowth (of the nature of a"replacement" fibrosis). This is true of the results recorded in the literature (p. 149) and of the results of our own experiments (p. 130, 143.).

The issue is thereby narrowed to a primary change in the arterioles, the glomeruli or the interstitial tissue or in a combination of these. Since the minor changes producible in animals are in the smaller arterioles and the glomeruli and chronic changes in the interstitial tissue are more uniformly absent, the experimental evidence taken as a whole, is slightly in favour of the first evidences of chronicity being the changes in the small arterioles and the glomerular tufts. Interstitial changes are probably subsequent to these and

largely caused by them. This is confirmatory of the fact already noted that human kidneys in which are found what are apparently the earliest stages of chronic changes, the alterations are glomerular and not interstitial.

It is not, of course, a universally acknowledged fact that there is any single sequence leading to contraction of the kidneys, and one type of contracted kidney, the arterio-sclerotic, is often described as if it were sharply demarcated from the others. We have already indicated that it is doubtful if a clear demarcation really exists (p. 74.).

We investigated the point a little more in a series of 70 consecutive post-mortems at Aberdeen Royal Infirmary last year. Eight of the seventy showed in the kidneys pretty marked naked eye evidence of that irregular type of contraction which is regarded as typical of the arterio-sclerotic kidney. The smaller renal vessels were thickened and prominent in all. Of these eight, four showed to the naked eye only very minor evidences of the more regular finer granularity etc. which are supposed to be characteristic of "chronic interstitial nephritis" as against arterio-sclerotic kidney. Nor did they show the loss of clear demarcation between the cortex and medulla of the cut surface which also is supposed to be specially characteristic of "chronic interstitial nephritis", or any great general thickening or adhesion of the capsule. The other four showed even naked

eye, distinct indication of admixture of the two conditions.

Nevertheless, microscopically, in all eight, marked chronic inflammatory changes were evident (concentric fibrosis around the glomeruli, or crescent formation or progressive glomerular changes where the afferent arterioles showed but little change etc. etc.). The histological diagnosis in all cases was "chronic interstitial nephritis" accompanied by a rather unusual degree of arterio-sclerotic atrophy.

In no kidney of the series was intra-renal arterio-sclerosis found unaccompanied microscopically by chronic inflammatory renal changes.

In four of the seventy cases, relatively normal kidneys were found although advanced atheroma had been noted in the aorta and main renal artery. The smaller renal vessels showed only a very slight degree of arterio-sclerosis (no nodular atheroma).

In five of the eight "arterio-sclerotic" kidneys previously referred to there was marked atheroma of the aorta, but in only one of these was the main renal artery involved at all severely.

These figures point to a much closer relationship of sclerosis of the smaller renal vessels to renal inflammatory change than to generalised arterial degenerations.

Not only are we thus compelled to admit a

greater haziness as to the sequence of development of chronic than of acute nephritis, but it is more difficult also here to get convincing evidence of the causation, largely for the same reason - that it has not been successfully produced experimentally. We are relying for our evidence on this point mainly on (1) the bacteriological results of clinical investigation (p. 57) (2) clinical observations of the coincidence of chronic nephritis and chronic focal sepsis (p. 59.) (3) the fact that it may be an undoubted sequel of acute nephritis, where we have more satisfactory evidence of bacterial or toxic causation. With regard to the last fact we infer that the actue case does not clear up but goes on to chronic manifestations, if and when an original distributing focus of bacteria and toxins persists in an active though possibly subacute or chronic form. The difficulty of producing chronic nephritis experimentally supplies us with strong evidence that even the most fulminated renal changes do <u>not</u> necessarily involve much in the way of permanent structural damage if the patient survives. If that be true, the distributing focus (now becoming a site of "chronic focal sepsis") must persist before we can get chronic changes.

We have not much further to go beyond this standpoint to infer that insidiously arising chronic nephritis also is derived by embolism and toxaemia from focal sepsis, without an acute phase.

Analogy with a particular form of chronic

nephritis strengthens our view as to the causation in the ordinary insidious case. This form is the chronic focal embolic glomerulo-nephritis of subacute endocarditis. It has already been discussed (p. 61 p. 164), and our conclusions was that it differed from other cases of chronic nephritis chiefly in particulars which might be explained simply by a difference in the size of the emboli, and in the less purely mechanical action of these emboli in the diffuser chronic nephritis cases (less infarction; more inflammation).

Probably the most important practical deduction from our observations on the etiology of nephritis bears on the treatment of the disease.

If the cause is focal sepsis (or, sometimes, in acute nephritis, acute infections), the most important point both in prophylaxis and treatment comes to be the eradication of such focal sepsis.

Moreover, if we are right as to the mechanism of causation, such eradication is even more important and more hopeful than in many other diseases in which also focal sepsis may have been the original cause. Where a disease arises by bacterial metastasis from a septic focus elsewhere, with multiplication of the bacteria in the metastatic site, removal of the original focus, even if complete, may have little effect. Whereas if, as in the case of nephritis, a disease arises from and is sustained by toxaemia with merely bacterial embolism and lysis from such a focus, complete eradication of the focus

is equivalent to arrest of the secondary disease. In other words, eradication of focal sepsis in nephritis is specially hopeful because it is unlikely that there is any focus of bacterial multiplication in the kidneys themselves (p. 49.).

Correlation of Clinical and Post-mortem Findings in Nephritis.

We think it may be of some interest to conclude the thesis with some reference to the all important problem of the correlation of clinical and post-mortem findings.

Such a discussion should, we think, begin with the admission that the difficulty in classification is much more often pathological than clinical. There are several well defined disease-syndromes in nephritis, and it is the failure to find uniform post-mortem appearances in cases clearly belonging clinically to a well defined group that is puzzling.

Our reason for venturing to approach this task at all lies in our belief that in reviewing the characteristic"clinical syndrome" of chemical nephritis, we were in reality obtaining, so to speak, the type syndrome of the only pure tubular nephritis which exists (p. 149).

Bearing this syndrome in mind, we hope, with the assistance of the modern theory of renal function to be able to assess, from the differences and resemblances of other syndromes to this one, the degree and type of tubular damage, and to be able to affirm to some extent what must in each syndrome be the type of the coexisting glomerular lesions.

The theoretical types of renal change which we have, on these grounds, postulated for the various clinical syndromes, have, in their broad features, fitted in pretty well with the appearances found in the nephritic kidneys we have examined in the last two years.

We have two preliminary observations to make as to the nature of the criteria we are using in determining the clinical history of the kidneys examined.

In the first place, these criteria are histological. The rather hazardous diagnoses which are dependent on naked eye appearances (colour, size, etc.) fail very frequently.

The source of error is not hard to find, for the naked eye appearances are not always associated with the histological changes which one expects.

In the second place, we will focus our attention largely on a particular part of the histology of the organ. We will almost ignore the amount of interstitial change present. This has a theoretical justification. Whether or not a kidney is functionally efficient must eventually be determined by the number and activity of the surviving units - i.e. glomeruli and tubules; and to these, consequently, we will almost confine our attention.

A practical justification for this attitude also exists. Of the two main clinical types of chronic nephritis, the hydraemic and the azotaemic, the latter is the one usually associated with the more interstitial change. Indeed, the clinician sometimes refers to it as chronic interstitial nephritis. Yet some cases of hydraemic nephritis may show more interstitial increase than some of azotaemic nephritis. No diagnosis, therefore, which rests upon the amount of interstitial change is likely to be accurate.

We will now attempt the correlation of three clinical varieties of nephritis with histological appearances. The first is acute nephritis, the others are the"hydraemic" ("parenchymatous") and"azotaemic" ("interstitial") types of chronic nephritis.

Correlation of Histological Changes and Clinical Observations in Acute Nephritis.

Here a glomerular hyperpermeability coexists at first with a glomerular stasis. Hence arises the anuria, followed by oliguria and albuminaria. In these cases, the filtrate is not simply halved. This need not even lead to oliguria (as we shall see under azotaemic nephritis p.299). Filtration is suspended. This causes anuria and on partial resumption of filtration, the damaged glomerular membranes allow albumen also to get through. Both diminution of filtrate and later tubular desquamative changes (with mechanical "seeping back" of urea into the circulation) combine to raise the blood urea. Oedema may be partly due to loss of albumen and lowered osmotic pressure in the blood, but as it often appears very early, before much albumen has been lost, it is probably more closely related to toxic changes in the endothelium of the capillaries generally.

Correlation of Histological Changes and Clinical Observations in Hydraemic Nephritis.

The clinician who has found the well known clinical syndrome of hydraemic or parenchymatous nephritis during life is sometimes surprised to learn that post-mortem examination shows marked glomerular changes also. We believe that, as a matter of fact, kidneys producing the clinical picture of parenchymatous nephritis invariably show important glomerular alterations, and further, we, in view of the symptoms during life, believe that this is only to be expected. The clinical syndrome is not that of a tubular nephritis i.e. is not the syndrome we have described in the only true tubular nephritis - chemical nephritis (p.149). Doubtless, it has many resemblances due to involvement of the tubules. but also it shows many differences, due to the glomerular changes.

We shall now discuss the chief features of the clinicians' "parenchymatous' nephritis and endeavour to

explain them. We shall then be obliged to conclude that the syndrome is by no means explained on the supposition that it indicates the presence of a purely tubular nephritis.

Parenchymatous nephritis shows typically (a) only moderately raised blood ures, (b) often enough a prolonged course before there is any development of uraemic symptoms, (c) prolonged, often copious, albuminuria, (d) marked oedema, (e) marked chloride retention.

For (a) and (b) tubular damage is responsible, and, as this is the case the changes are similar to those in chemical nephritis. The urea, and to a less extent the creatinin, is allowed by the catarrhal tubules to "seep back" mechanically from the filtrate (p. 150). The glomerular changes in clinical parenchymatous nephritis probably do not greatly contribute to the urea retention, for they tend to cause <u>hyperpermeability</u>, rather than impermeability.

(c) Here, (as regards albuminuria), we have a contrast between chemical and hydraemic nephritis. Tubular nephritis gives a mild albuminuria due to tubular debris. Such tubular debris is present in clinical parenchymatous nephritis also, but there is in addition a large amount of albumen being constantly lost through the inflamed hyperpermeable glomeruli. How can we blame the tubules for a loss of albumen which may in the course of the disease reach a total greater than the kidney weights?

(d) Oedema is not a constant feature of tubular (chemical) nephritis. When present, it is due to causes outside the tubules. (p. 151). It is a constant feature of clinical parenchymatous nephritis. This may be explained by the superadding of the factor already referred to - copious loss of albumen from the plasma through inflamed glomeruli, and lowered osmotic pressure of the blood.

(e) As regards salt retention, the results have been described as a more or less constant retention in clinical parenchymatous nephritis, and as being very variable in true tubular nephritis.

Now, as oedema is considerable and constant only in the clinical type, it may be held to be responsible for the salt retention there. We take this view, in spite of the possibility of its being regarded as "putting the cart before the horse", because we are unable to understand the rationale of the usual opposite sequence. How is it, that if we regard such kidneys as unable to excrete salt,

we have explained the "resultant" oedema? The immediate result, as far as we can see, of inability of the kidneys to excrete salt would be to raise the salt content of the plasma, thereby raising its osmotic pressure, and rendering more difficult the passage of fluid from the capillaries to the tissues.

In chemical nephritis, we have no severe albuminuria, and therefore no necessary oedema and resultant salt retention. Nor can we claim that the salt retention cases recorded are invariably oedematous ones.

If we follow blindly the reasoning we have already adopted in relation to urea and creatinin (see chemical nephritis p. 150), we might reach a very peculiar conclusion. We have indicated a belief that, as urea has a higher threshold than creatinin, the damaged tubular cells will naturally cease to form an adequate barrier against excessive reabsorption of urea sooner than against creatinin. On superficial examination, one might conclude that since salt has a much higher threshold than either urea or creatinin it would always be the first of the three to be too much reabsorbed, and the first therefore to be"retained".

But the threshold for chloride is so high that a new factor has come into operation altogether alters the problem.

Under certain quite physiological conditions, (e.g. low chloride intake or diuresis), the concentration of chloride in the urine may be lower than that in the plasma. This, of course, can never physiologically occur with lower threshold bodies such as urea. Taking such a case where the chloride in the urine is for physiological reasons lower than that in the plasma, we note that the filtrate will as always contain chloride in exactly the same original concentration as does the plasma, namely a low concentration in this case. The tubules, however, automatically correct the plasma content, for the fluid they reabsorb from the filtrate ("modified Locke's solution" of Cushny) is richer in chloride than the filtrate itself. Naturally, therefore, the urine comes to have chloride in lesser concentration than the plasma. Of course, where the conditions are opposite, say excessive salt intake, the relation of urine and plasma chlorides will be emphatically reversed.

Here we have a possible key to apparently erratic variation in salt metabolism in a pure tubular nephritis. We admit, as a logical sequel to our views on the order of failure of urea and creatinin excretion,

that the tubular mechanism fails earliest of all in relation to salt. But the result is not necessarily salt retention. In these circumstances where the urine should physiologically contain less salt than the plasma, the fluid which would mechanically "seep" back through damaged tubules, would be less rich in salt than the physiologically reabsorbed fluid, and no chloride retention could result. Yet, in other circumstances, some retention might take place (e.g. in increased salt intake, where a concentrated filtrate might "seep" back into the bloodstream).

One concludes that the frequently expressed difficulty of correlating clinical and post-mortem observations in clinical parenchymatous nephritis lies largely in the incorrect assumption that the clinical syndrome is suggested of tubular changes only. The name parenchymatous nephritis seems to be a very bad one, and the alternative "hydraemic" might well completely replace it.

The histological changes we regard as typical of hydraemic nephritis are

(a) tubular catarrh,

and (b) glomerular inflammation with hyperpermeability.

Correlation of Histological Changes and Clinical Observations in Azotaemic Nephritis.

Let us first set down the headings which roughly distinguish an azotaemic nephritis clinically. (We reject the term "chronic interstitial nephritis" for this clinical syndrome just as we rejected the term "chronic parenchymatous nephritis" for the "hydraemic" syndrome. Interstitial changes may be more marked in some cases of hydraemic nephritis than they are in some of azotaemic nephritis).

(a) Very high blood urea. (b) Polyuria. (c) An ever present danger of uraemia. (d) No albuminuria or only an occasional trace. (e) No oedema. (f) Little or no chloride retention.

Now, if there is a single type of kidney lesion of the usual pathological classifications pre-eminently

associated with such a syndrome, it is the severer examples of "small red kidney". The association is by no means constant, however, and we wish to suggest on theoretical grounds, and from information obtained by examination of kidneys post-mortem, that the following histological picture might show a greater frequency of association with azotaemic nephritis during life than any naked eye type.

In the kidney we refer to there may or may not be contraction. The amount of interstitial change is quite inconstant; but there is microscopically marked diminution in the number of functioning renal units. There is not necessarily or typically any acute tubular change, but the surviving tubules are very atrophic. Acute tubular changes, when present, are terminal. They indicate a death precipitated by acute superadded on old changes, and they are not the changes which explain the signs and symptoms which were present during the lengthy course which preceded the terminal "acute nephritis".

At the same time there are marked glomerular changes. These are of fibrotic nature or marked by the presence of well developed epithelial crescents. In a word, the glomeruli are impermeable.

Although the coexistence of such glomerular and tubular changes is more usually found in a small red kidney than in many others, they may not be present in such a kidney, and may be present in kidneys of other types. In such cases we would take the histological picture as our guide to diagnosis.

How could a kidney with (a) many impermeable glomeruli and (b) a reduced number of tubules, mostly atrophic, cause the syndrome of azotaemic nephritis?

Let us, as with the hydraemic type previously, deal with the signs and symptoms one by one.

(a) Very high blood urea. Glomerular fibrosis greatly reduces the filtrate and so the total urea which can be excreted is much lower than normal. The blood urea rises as a result. When it has attained a very considerable height, as it often does, a normal daily total of urea may be excreted in the urine. This has been repeatedly observed. It simply means that though the filtrate is diminished in quantity it naturally contains a higher percentage of urea, since in glomerular infiltration crystalloids pass through in the same concentration as they show in the plasma. We would emphasise the word "filtrate" in this connection. The concentration of urea in the urine in azotaemic nephritis is typically lowered because the poor

reabsorbing power of the atrophic tubules more than balances the initial higher concentration in the filtrate.

(b) Polyuria. We introduce this here, for it leads to an immediate, though very superficial objection, to the reasoning under (a). If the filtrate be, say, halved, we have every reason for a progressive rise in the blood urea, (until, as said, a great"head"of urea is obtained in the plasma). At the same time, we have no reason at all to expect a diminution in the amount of urine. The calculated and the observed proportion of filtrate to urine is, as has been indicated repeatedly, very high indeed, something in the neighbourhood of 120 to 1, and the halving of the filtrate is therefore consistent with a polyuria if the tubular reabsorption be deficient; and here tubular reabsorption by the atrophic poorly functioning cells of the tubules must be deficient.(See Cushny 33.).

(c) Uraemia may be connected with diminution of the filtrate; but uraemia will remain a difficulty in any explanation whilst its own precise nature remains unknown.

(d) No albuminuria. The glomeruli are not hyperpermeable, and the tubules are not catarrhal.

(e) No oedema. There is no lowering of the osmotic pressure of the blood, for there is no albuminuria. Moreover, injury to the general capillaries is less likely than in the hydraemic condition, for, in the latter, and not here there is evidence of toxic damage to endothelium (as indicated by the hyperpermeable glomeruli).

(f) Little or no salt retention. Salt under normal circumstances is largely conserved by the body i.e. it forms a normal important part of the reabsorbed fluid. Hence two antagonising factors tend to nullify one another. The diminished filtrate diminishes salt output from the plasma, but diminish^ed reabsorption by the atrophic tubular cells tends to leave in the urine an unusual proportion of such salt as is filtered.

These correlations have been dogmatically expressed. They are probably in detail inadequate and even incorrect. But they fit in to a degree sufficient to warrant consideration. They afford abundant proof that the main clinical types of chronic nephritis cannot be divided into glomerular and tubular. They suggest that an investigation of the histology of the organ, ignoring the naked eye appearances, and even ignoring the amount of interstitial change may often enable the pathologist to type the case more correctly from a clinical point of view.

Whatever may be the degree of truth in our classification, we feel that at least it is true that

(a) hydraemic nephritis is not purely parenchymatous, but that some of its essential features e.g. albuminuria, are definitely dependent on important glomerular alterations; and that

(b) azotaemic nephritis differs from the other, not in the presence but in the type of glomerular alteration, and shows, like the other form, important alterations in the tubules, though these also are of a different nature.

SUMMARY OF SECTION 2.

1. The literature on experimental chemical and bacterio-toxic nephritis is abstracted and critically reviewed.

2. The author's experiments with substances of both groups are recorded and considered.

3, "Chemical" nephritis is always at the start essentially a tubular nephritis, and is so because the chemical molecules are simple and filterable and are concentrated in the tubules to a degree which more than counteracts any selectivity for other tissues.

4. Apart from "chemical" nephritis, there is no pure tubular nephritis.

5. Experimentally, bacterial or bacterio-toxic nephritis selectively attacks the glomeruli. It produces its changes by the action of exotoxins and of endotoxins. The latter are derived by lysis of organisms trapped in the glomeruli, the former are concentrated in the glomeruli by the withdrawal of fluid into the filtrate. This is possible because the toxins, unlike crystalloid chemicals, are colloids, and do not pass through the undamaged glomerular filter.

6. The changes in bacterial or bacterio-toxic nephritis are at first endoglomerular, then endoglomerular and epiglomerular, and still later severe tubular lesions develop.

7. These later tubular lesions may be simply the direct result of continued action of dilute toxin from the bloodstream on highly organised cells, but the tubules may be exposed also in later stages to a concentrated toxin in the filtrate, for the initial damage to the tufts destroys their efficient action as a semi-permeable membrane. Of this fact, albuminuria, derived from the bloodstream through the tufts, is evidence.

8. Until this glomerular hyperpermeability develops as a result of damage, the tubules are naturally exposed only to much the same concentration of the toxin as are most other body cells, because the concentrated toxin in the glomerular capillaries is rapidly rediluted by return of fluid reabsorbed from the filtrate.

9. "Tubular" nephritis found post-mortem represents, not a different initial type of attack, but a later stage of the disease, a stage at which there may actually have been considerable retrogression of the original glomerular lesions. This is because, just in so far as the glomeruli become toxin-permeable,

the special concentration of toxin in them decreases.

10. The organisms best adapted to cause nephritis are those which form a large amount of endotoxin and of exotoxin, and which give rise on occasion to bacteriaemia as well as to toxaemia.

11. The organism which most completely fills this role is the streptococcus.

12. Acute interstitial nephritis is the only nephritis where the facts rather suggest a local multiplication of organisms in the kidneys, and therein probably lies the reason for its distinction from other cases of acute nephritis.

13. Minor but quite distinctive differences are recorded between the experimental nephrides we have produced with diphtheria toxin and streptococcal toxin.

14. Marked chronic nephritis has not at any time been successfully produced in animals. The initial glomerular changes for the most part retrogress. They cannot be made more progressive by simulation of chronic septic absorption by any method of administration yet tried. We failed by methods designed to give a nearly continuous administration. We failed similarly when we injected in turn a variety of organisms and toxins into the same animal in the hope of preventing immunisation.

15. It is unlikely that chronic septic absorption, the cause of insidiously arising chronic nephritis in man, can be simulated by administration of substances from outside, for there is no guarantee that the immunity reactions are not keeping pace with the administration.

16. If it were possible to create and maintain a chronic septic focus, preferably streptococcal, in an animal, the method would be much more hopeful, for the maintenance of the focus would in itself be evidence of inadequate immunisation.

17. The literature on experimental nephritis is full of descriptions of "chronic nephritis" which are really of palpably spontaneous type.

18. A modified non-diffuse chronic nephritis simulating that in subacute bacterial endocarditis has been successfully produced in animals, and a discussion of its features lends force to the view that insidiously arising chronic nephritis does arise by bacterial bombardment of the kidneys by organisms of low virulence from chronic septic foci.

19. An attempt has been made to correlate histological changes with the clinical syndromes of the chief groups of nephritis.

20. Arterio-sclerosis in the smaller renal vessels is an accompaniment and a manifestation of nephritis, and is not a separate atrophic process occurring in generalised arterio-sclerosis.

21. The sequence of changes in the production of chronic nephritis is believed to be probably somewhat as follows:-

(a) Early chronic changes are first seen in and around the afferent arterioles and glomeruli.

(b) These may increase, with or without considerable resultant interstitial change, whilst many of the glomeruli continue to suffer from toxic changes analogous to those in the acute stage, and whilst the tubules remain catarrhal from the same toxic action. In such cases the syndrome of hydraemic nephritis results.

(c) If, on the other hand, the increase of these initial chronic changes is not accompanied by further acute toxic changes in either glomeruli or tubules, but simply leads to progressive glomerular impermeability and hence tubular atrophy, we get the clinical syndrome of azotaemic nephritis.

(d) The latter form may also arise insidiously by repeated bacterial embolism from chronic septic foci.

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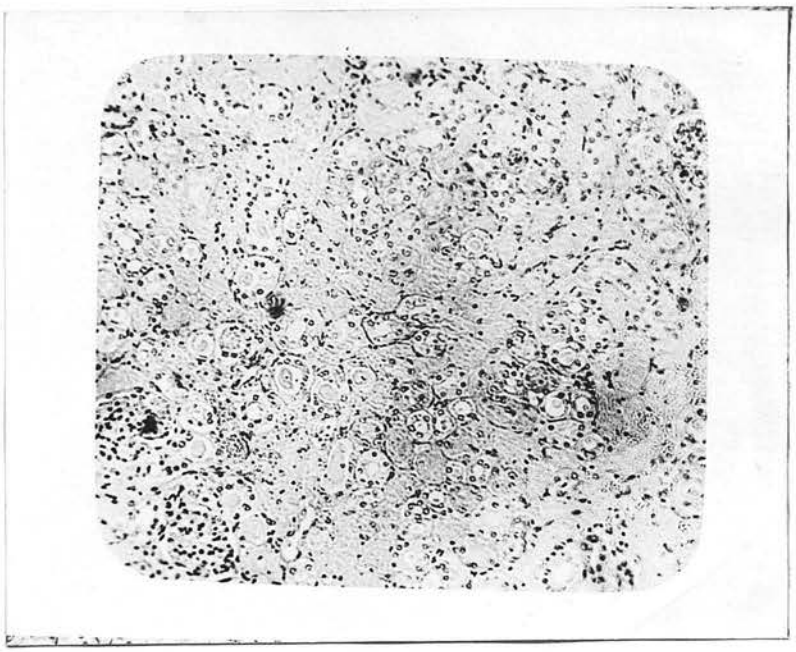
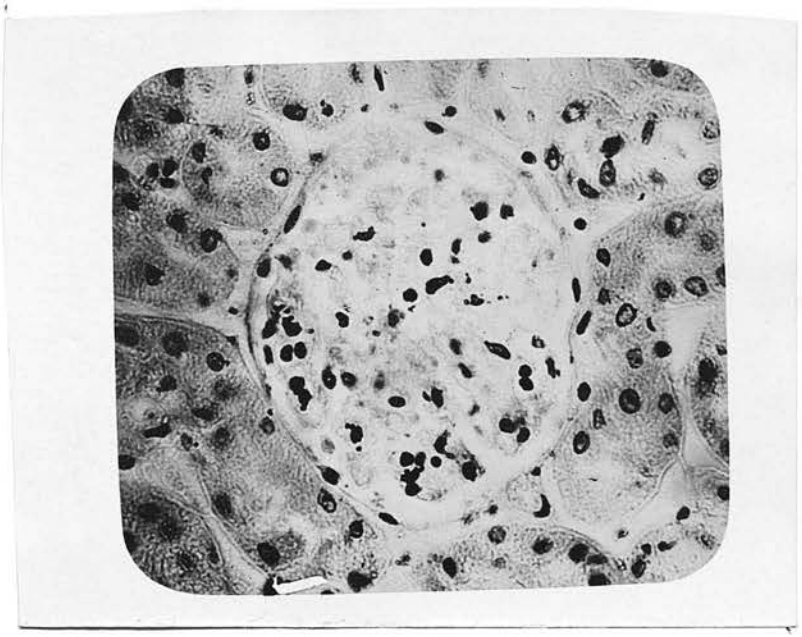
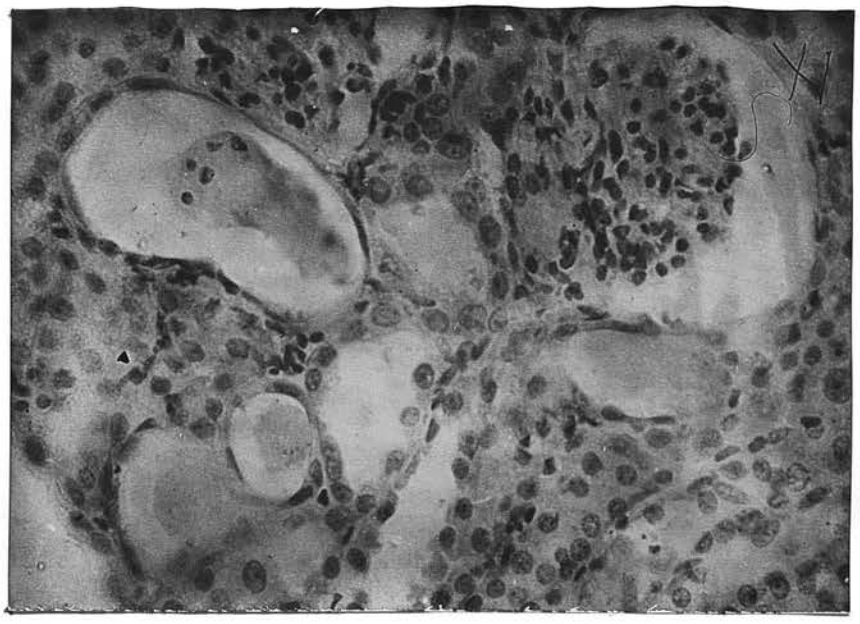


Microphotograph 1.(x 120). Rabbit C.
Necrosis of convoluted tubules, with block of lumen and loss of nuclei in many places; casts, chiefly in collecting tubules; less glomerular change.

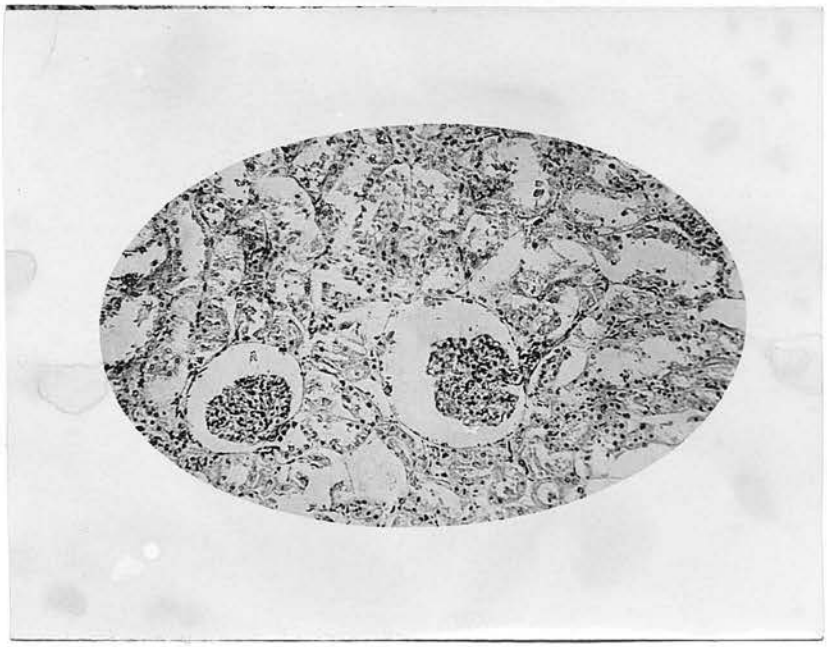
Microphotograph 2. (x 400). Rabbit C.
Shows necrotic tubules with swollen necrotic cells filling up the lumen, and loss of epithelial nuclei; cast formation. The glomerulus picked out here shows more change than most glomeruli- swelling of endothelial nuclei, and particularly of nuclei of the covering epithelium.



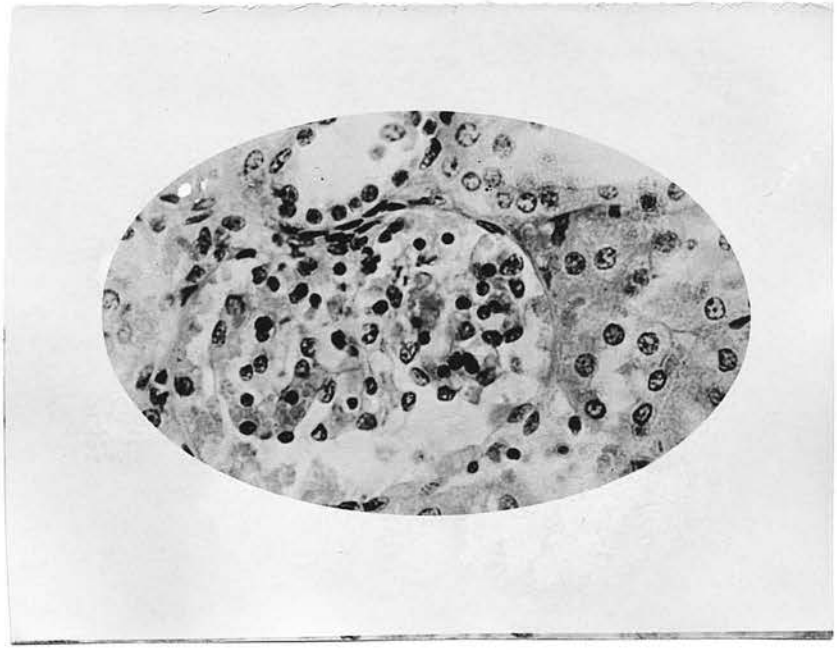
Microphotograph 3. (x 400). Rabbit F.
Tubular degeneration and necrosis. Disappearance of many glomerular endothelial nuclei, karyorrhexis of others; disappearance of much of tuft epithelium.



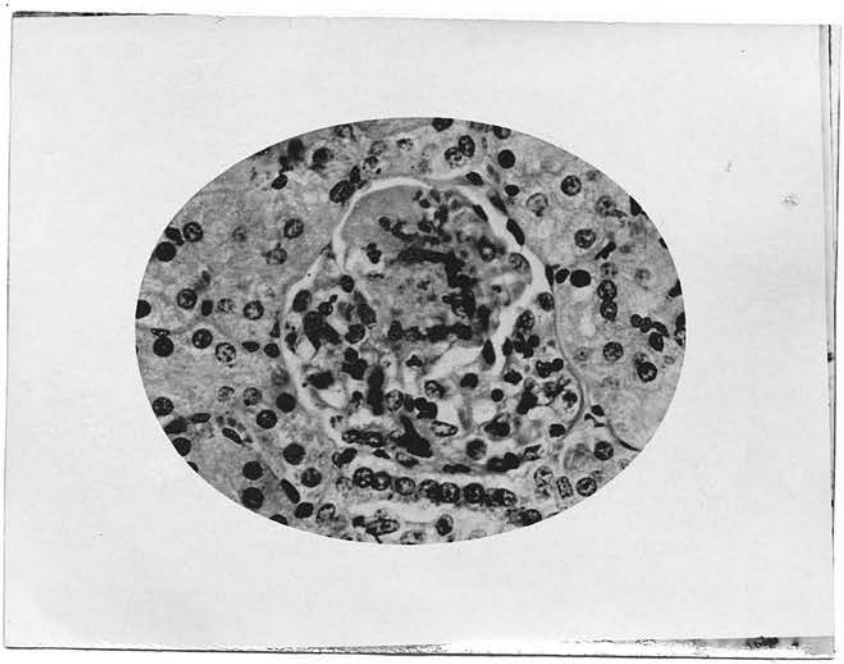
Microphotograph 4. (x400). Rabbit V.
Condensation and shrinkage of glomerulus without any fibrosis. Atrophy of tubular epithelium. Casts- one obviously in process of formation from desquamated epithelium. No increase of interstitial tissue.



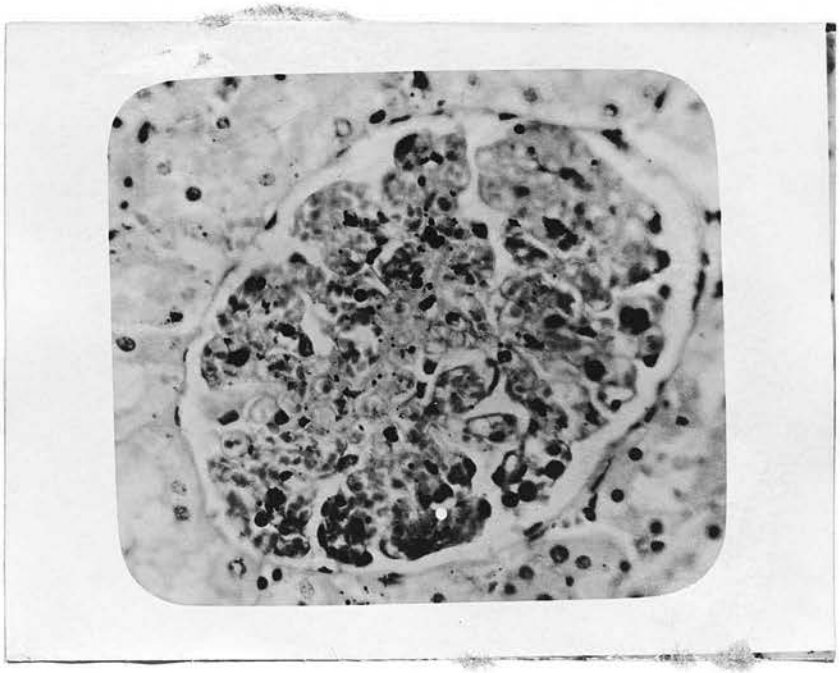
Microphotograph 5. (x 120). Rat 6.12.
Some shrinkage of glomeruli, with dilatation of capsular spaces. Catarrh and atrophy of tubules.



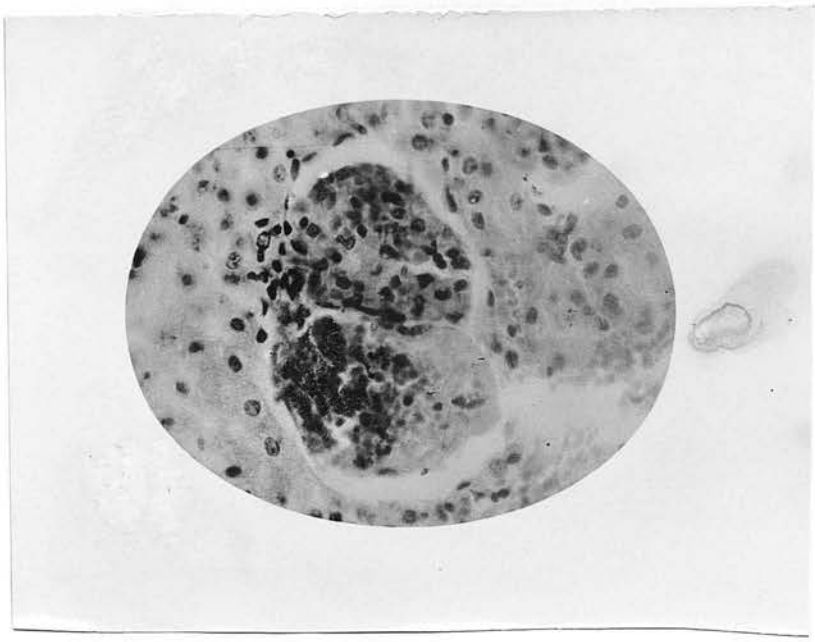
Microphotograph 6. (x400). Rabbit 5.
Glomerulus showing swelling and, in one or two places, karyorrhexis, of endothelial nuclei. The epithelium covering the tuft is swollen and prominent and there is some albumen in the capsular space. Some swelling of parietal epithelium; slighter tubular changes.



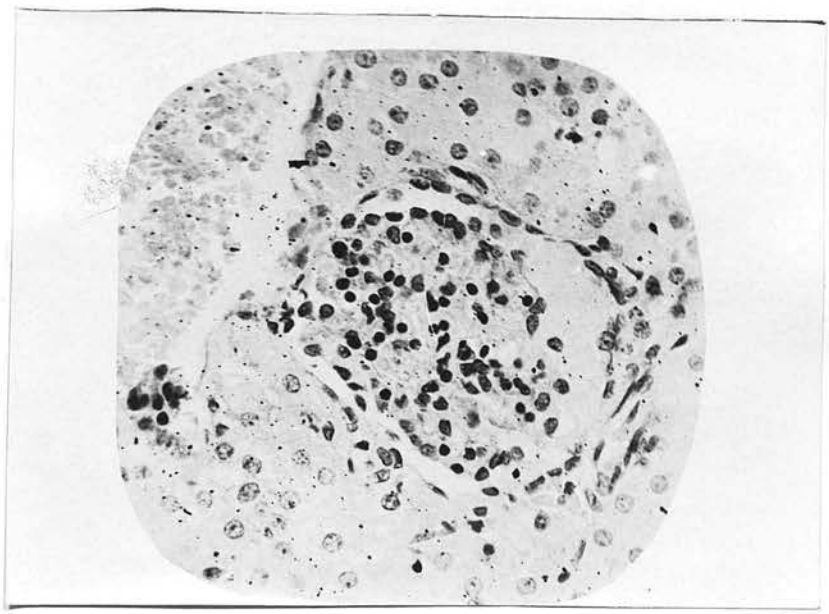
Microphotograph 7. (x 400). Rabbit T.
Swelling of endothelium of glomerulus. Some karyorrhexis of the endothelium. "Blood-cyst" in upper half. Tubules relatively normal.



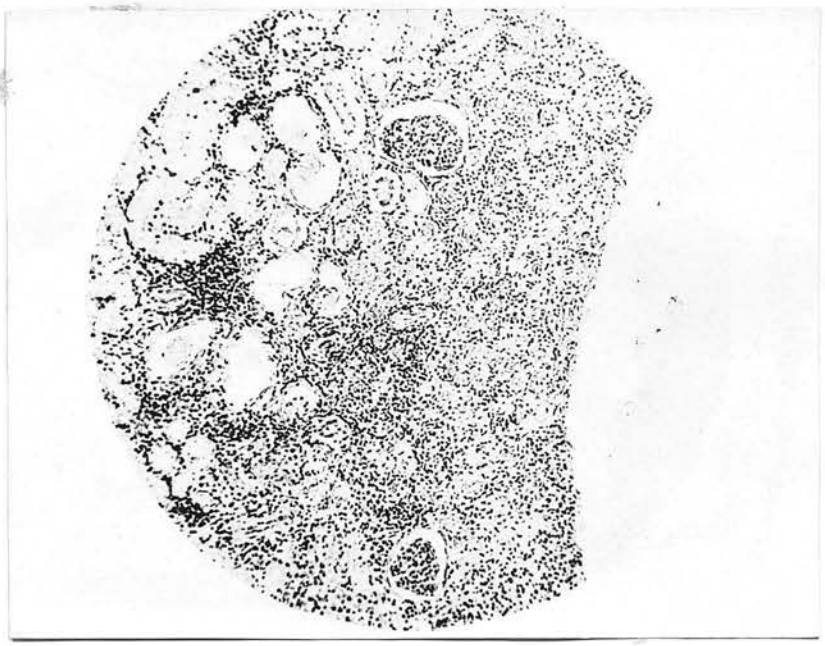
Microphotograph 8. (x 600). Rabbit G.
Great congestion and distension of glomeruli. Disappearance of some endothelial nuclei. Karyorrhexis of other endothelial nuclei. Lesser changes in the tubules.



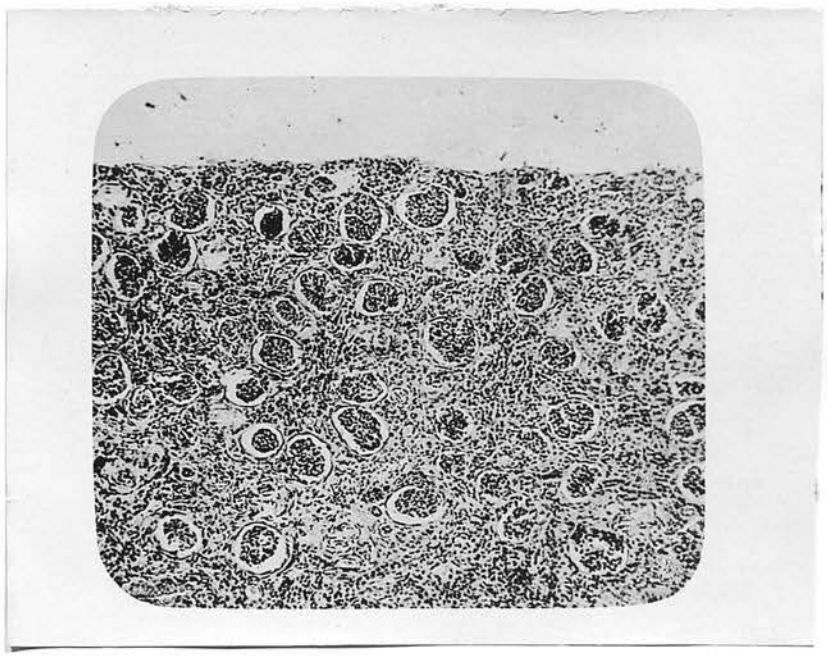
Microphotograph 9. (x 400). Rabbit M.
Glomerulus showing lower half converted into "blood-cyst", with endothelium stretched out over it. Lesser changes in the tubules.



Microphotograph 10. (x 400). Rabbit W.
Showing congestion, some swelling of endothelial nuclei, slight endothelial karyorrhexis. Swelling of epithelium covering tuft, albuminous material in capsular spaces. Tubules almost normal.



Microphotograph 11. (x 120). Rabbit U.
Spontaneous Nephritis. Focal areas of round celled infiltration under capsule. Depression of capsule. Glomeruli almost normal. Tubules atrophic,-either dilated and containing casts or small and made out with difficulty from surrounding round cells.



Microphotograph 12. (x 120). Rabbit Y.
Spontaneous Nephritis. As in "11", the glomeruli are relatively normal. The tubules are atrophic and shrunken, and are made out with difficulty amongst round celled infiltration.